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(54) Title: COMPOSITIONS AND METHODS RELATING TO OVARIAN SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acid molecules and polypeptides present in normal and neoplastic ovarian cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions containing the nucleic acid molecules, polypeptides, antibodies, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating ovarian cancer and noncancerous disease states in ovarian, identifying ovarian tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered ovarian tissue for treatment and research.

WO 2004/013311 A2

COMPOSITIONS AND METHODS RELATING TO OVARIAN SPECIFIC GENES AND PROTEINS

FIELD OF THE INVENTION

The present invention relates to newly identified nucleic acids and polypeptides present in normal and neoplastic ovarian cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions comprising the nucleic acids, polypeptides, antibodies, post translational modifications (PTMs), variants, derivatives, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating ovarian cancer and non-cancerous disease states in ovarian, identifying ovarian tissue and monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, therapeutic molecules including but limited to antibodies or antisense molecules, production of transgenic animals and cells, and production of engineered ovarian tissue for treatment and research.

BACKGROUND OF THE INVENTION

Cancer of the ovaries is the fourth-most common cause of cancer death in women in the United States, with more than 23,000 new cases and roughly 14,000 deaths predicted for the year 2001. Shridhar, V. et al., *Cancer Res.* 61(15): 5895-904 (2001); Memarzadeh, S. & Berek, J. S., *J. Reprod. Med.* 46(7): 621-29 (2001). The incidence of ovarian cancer is of serious concern worldwide, with an estimated 191,000 new cases predicted annually. Runnebaum, I. B. & Stickeler, E., J. *Cancer Res. Clin. Oncol.* 127(2): 73-79 (2001). Unfortunately, women with ovarian cancer are typically asymptomatic until the disease has metastasized. Because effective screening for ovarian cancer is not available, roughly 70% of women diagnosed have an advanced stage of the cancer with a five-year survival rate of ~25-30%. Memarzadeh, S. & Berek, J. S., *supra*; Nunns, D. et al., *Obstet. Gynecol. Surv.* 55(12): 746-51. Conversely, women diagnosed with early stage ovarian cancer enjoy considerably higher survival rates. Werness, B. A. & Eltabbakh, G. H., *Int'l. J. Gynecol. Pathol.* 20(1): 48-63 (2001). Although our understanding of the etiology of ovarian cancer is incomplete, the results of extensive research in this area point to a combination of age, genetics, reproductive, and

dietary/environmental factors. Age is a key risk factor in the development of ovarian cancer: while the risk for developing ovarian cancer before the age of 30 is slim, the incidence of ovarian cancer rises linearly between ages 30 to 50, increasing at a slower rate thereafter, with the highest incidence being among septagenarian women. Jeanne M. Schilder et al., Hereditary Ovarian Cancer: Clinical Syndromes and Management, in Ovarian Cancer 182 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001).

With respect to genetic factors, a family history of ovarian cancer is the most significant risk factor in the development of the disease, with that risk depending on the number of affected family members, the degree of their relationship to the woman, and which particular first degree relatives are affected by the disease. *Id.* Mutations in several genes have been associated with ovarian cancer, including BRCA1 and BRCA2, both of which play a key role in the development of breast cancer, as well as hMSH2 and hMLH1, both of which are associated with hereditary non-polyposis colon cancer. Katherine Y. Look, Epidemiology, Etiology, and Screening of Ovarian Cancer, in Ovarian Cancer 169, 171-73 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001). BRCA1, located on chromosome 17, and BRCA2, located on chromosome 13, are tumor suppressor genes implicated in DNA repair; mutations in these genes are linked to roughly 10% of ovarian cancers. *Id.* at 171-72; Schilder et al., *supra* at 185-86. hMSH2 and hMLH1 are associated with DNA mismatch repair, and are located on chromosomes 2 and 3, respectively; it has been reported that roughly 3% of heriditary ovarian carcinomas are due to mutations in these genes. Look, *supra* at 173; Schilder et al., *supra* at 184, 188-89.

Reproductive factors have also been associated with an increased or reduced risk of ovarian cancer. Late menopause, nulliparity, and early age at menarche have all been linked with an elevated risk of ovarian cancer. Schilder et al., *supra* at 182. One theory hypothesizes that these factors increase the number of ovulatory cycles over the course of a woman's life, leading to "incessant ovulation," which is thought to be the primary cause of mutations to the ovarian epithelium. *Id.*; Laura J. Havrilesky & Andrew Berchuck, Molecular Alterations in Sporadic Ovarian Cancer, in Ovarian Cancer 25 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001). The mutations may be explained by the fact that ovulation results in the destruction and repair of that epithelium, necessitating increased cell division, thereby increasing the possibility that an undetected mutation will occur. *Id.* Support for this theory may be found in the fact pregnancy, lactation, and the

use of oral contraceptives, all of which suppress ovulation, confer a protective effect with respect to developing ovarian cancer. *Id.*

Among dietary/environmental factors, there would appear to be an association between high intake of animal fat or red meat and ovarian cancer, while the antioxidant Vitamin A, which prevents free radical formation and also assists in maintaining normal cellular differentiation, may offer a protective effect. Look, *supra* at 169. Reports have also associated asbestos and hydrous magnesium trisilicate (talc), the latter of which may be present in diaphragms and sanitary napkins. *Id.* at 169-70.

Current screening procedures for ovarian cancer, while of some utility, are quite limited in their diagnostic ability, a problem that is particularly acute at early stages of cancer progression when the disease is typically asymptomatic yet is most readily treated. Walter J. Burdette, Cancer: Etiology, Diagnosis, and Treatment 166 (1998); Memarzadeh & Berek, *supra*; Runnebaum & Stickeler, *supra*; Werness & Eltabbakh, *supra*. Commonly used screening tests include biannual rectovaginal pelvic examination, radioimmunoassay to detect the CA-125 serum tumor marker, and transvaginal ultrasonography. Burdette, *supra* at 166.

Pelvic examination has failed to yield adequate numbers of early diagnoses, and the other methods are not sufficiently accurate. *Id.* One study reported that only 15% of patients who suffered from ovarian cancer were diagnosed with the disease at the time of their pelvic examination. Look, *supra* at 174. Moreover, the CA-125 test is prone to giving false positives in pre-menopausal women and has been reported to be of low predictive value in post-menopausal women. *Id.* at 174-75. Although transvaginal ultrasonography is now the preferred procedure for screening for ovarian cancer, it is unable to distinguish reliably between benign and malignant tumors, and also cannot locate primary peritoneal malignancies or ovarian cancer if the ovary size is normal. Schilder et al., *supra* at 194-95. While genetic testing for mutations of the BRCA1, BRCA2, hMSH2, and hMLH1 genes is now available, these tests may be too costly for some patients and may also yield false negative or indeterminate results. Schilder et al., *supra* at 191-94.

The staging of ovarian cancer, which is accomplished through surgical exploration, is crucial in determining the course of treatment and management of the disease. AJCC Cancer Staging Handbook 187 (Irvin D. Fleming et al. eds., 5th ed. 1998); Burdette, *supra* at 170; Memarzadeh & Berek, *supra*; Shridhar et al., *supra*. Staging is performed by

reference to the classification system developed by the International Federation of Gynecology and Obstetrics. David H. Moore, Primary Surgical Management of Early Epithelial Ovarian Carcinoma, in Ovarian Cancer 203 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001); Fleming et al. eds., *supra* at 188. Stage I ovarian cancer is characterized by tumor growth that is limited to the ovaries and is comprised of three substages. *Id.* In substage IA, tumor growth is limited to one ovary, there is no tumor on the external surface of the ovary, the ovarian capsule is intact, and no malignant cells are present in ascites or peritoneal washings. *Id.* Substage IB is identical to A1, except that tumor growth is limited to both ovaries. *Id.* Substage IC refers to the presence of tumor growth limited to one or both ovaries, and also includes one or more of the following characteristics: capsule rupture, tumor growth on the surface of one or both ovaries, and malignant cells present in ascites or peritoneal washings. *Id.*

Stage II ovarian cancer refers to tumor growth involving one or both ovaries, along with pelvic extension. *Id.* Substage IIA involves extension and/or implants on the uterus and/or fallopian tubes, with no malignant cells in the ascites or peritoneal washings, while substage IIB involves extension into other pelvic organs and tissues, again with no malignant cells in the ascites or peritoneal washings. *Id.* Substage IIC involves pelvic extension as in IIA or IIB, but with malignant cells in the ascites or peritoneal washings. *Id.*

Stage III ovarian cancer involves tumor growth in one or both ovaries, with peritoneal metastasis beyond the pelvis confirmed by microscope and/or metastasis in the regional lymph nodes. *Id.* Substage IIIA is characterized by microscopic peritoneal metastasis outside the pelvis, with substage IIIB involving macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension. *Id.* Substage IIIC is identical to IIIB, except that the metastasis is greater than 2 cm in greatest dimension and may include regional lymph node metastasis. *Id.* Lastly, Stage IV refers to the presence distant metastasis, excluding peritoneal metastasis. *Id.*

While surgical staging is currently the benchmark for assessing the management and treatment of ovarian cancer, it suffers from considerable drawbacks, including the invasiveness of the procedure, the potential for complications, as well as the potential for inaccuracy. Moore, *supra* at 206-208, 213. In view of these limitations, attention has turned to developing alternative staging methodologies through understanding differential gene expression in various stages of ovarian cancer and by obtaining various biomarkers

to help better assess the progression of the disease. Vartiainen, J. et al., *Int'l J. Cancer,* 95(5): 313-16 (2001); Shridhar et al. *supra*; Baekelandt, M. et al., *J. Clin. Oncol.* 18(22): 3775-81.

The treatment of ovarian cancer typically involves a multiprong attack, with surgical intervention serving as the foundation of treatment. Dennis S. Chi & William J. Hoskins, Primary Surgical Management of Advanced Epithelial Ovarian Cancer, in Ovarian Cancer 241 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001). For example, in the case of epithelial ovarian cancer, which accounts for ~90% of cases of ovarian cancer, treatment typically consists of: (1) cytoreductive surgery, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymphadenectomy, followed by (2) adjuvant chemotherapy with paclitaxel and either cisplatin or carboplatin. Eltabbakh, G.H. & Awtrey, C.S., Expert Op. *Pharmacother.* 2(10): 109-24. Despite a clinical response rate of 80% to the adjuvant therapy, most patients experience tumor recurrence within three years of treatment. *Id.* Certain patients may undergo a second cytoreductive surgery and/or second-line chemotherapy. Memarzadeh & Berek, *supra*.

From the foregoing, it is clear that procedures used for detecting, diagnosing, monitoring, staging, prognosticating, and preventing the recurrence of ovarian cancer are of critical importance to the outcome of the patient. Moreover, current procedures, while helpful in each of these analyses, are limited by their specificity, sensitivity, invasiveness, and/or their cost. As such, highly specific and sensitive procedures that would operate by way of detecting novel markers in cells, tissues, or bodily fluids, with minimal invasiveness and at a reasonable cost, would be highly desirable.

SUMMARY OF THE INVENTION

The present invention solves many needs in the art by providing nucleic acid molecules, polypeptides and antibodies thereto, variants and derivatives of the nucleic acids and polypeptides, agonists and antagonists that may be used to identify, diagnose, monitor, stage, image and treat ovarian cancer and non-cancerous disease states in ovarian; identify and monitor ovarian tissue; and identify and design agonists and antagonists of polypeptides of the invention. The invention also provides gene therapy, methods for producing transgenic animals and cells, and methods for producing engineered ovarian tissue for treatment and research.

One aspect of the present invention relates to nucleic acid molecules that are specific to ovarian cells, ovarian tissue and/or the ovarian organ. These ovarian specific nucleic acids (OSNAs) may be a naturally occurring cDNA, genomic DNA, RNA, or a fragment of one of these nucleic acids, or may be a non-naturally occurring nucleic acid molecule. If the OSNA is genomic DNA, then the OSNA is a ovarian specific gene (OSG). If the OSNA is RNA, then it is a ovarian specific transcript encoded by a OSG. Due to alternative splicing and transcriptional modification one OSG may encode for multiple ovarian specific RNAs. In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that is specific to ovarian. More preferred is a nucleic acid molecule that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 249-396. In another preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1-248. For the OSNA sequences listed herein, DEX0443_001.nt.1 corresponds to SEQ ID NO: 1. For sequences with multiple splice variants, the parent sequence DEX0443_001.nt.1, will be followed by DEX0443_001.nt.2, etc. for each splice variant. The sequences off the corresponding peptides are listed as DEX0443_001.aa.1, etc. For the mapping of all of the nucleotides and peptides, see the table in the Example 1 section below.

This aspect of the present invention also relates to nucleic acid molecules that selectively hybridize or exhibit substantial sequence similarity to nucleic acid molecules encoding a Ovarian Specific Protein (OSP), or that selectively hybridize or exhibit substantial sequence similarity to a OSNA. In one embodiment of the present invention the nucleic acid molecule comprises an allelic variant of a nucleic acid molecule encoding a OSP, or an allelic variant of a OSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid sequence that encodes a OSP or a part of a nucleic acid sequence of a OSNA.

In addition, this aspect of the present invention relates to a nucleic acid molecule further comprising one or more expression control sequences controlling the transcription and/or translation of all or a part of a OSNA or the transcription and/or translation of a nucleic acid molecule that encodes all or a fragment of a OSP.

Another aspect of the present invention relates to vectors and/or host cells comprising a nucleic acid molecule of this invention. In a preferred embodiment, the nucleic acid molecule of the vector and/or host cell encodes all or a fragment of a OSP. In another preferred embodiment, the nucleic acid molecule of the vector and/or host cell

comprises all or a part of a OSNA. Vectors and host cells of the present invention are useful in the recombinant production of polypeptides, particularly OSPs of the present invention.

Another aspect of the present invention relates to polypeptides encoded by a nucleic acid molecule of this invention. The polypeptide may comprise either a fragment or a full-length protein. In a preferred embodiment, the polypeptide is a OSP. However, this aspect of the present invention also relates to mutant proteins (muteins) of OSPs, fusion proteins of which a portion is a OSP, and proteins and polypeptides encoded by allelic variants of a OSNA as provided herein.

A further aspect of the present invention is a splice variant which encodes an amino acid sequence that provides a region to be targeted for the generation of reagents that can be used in the detection and/or treatment of cancer. The amino acid sequence may lead to a unique protein structure, protein subcellular localization, biochemical processing or function. This information can be used to directly or indirectly facilitate the generation of additional or novel therapeutics or diagnostics. The nucleotide sequence in this splice variant can be used as a nucleic acid probe for the diagnosis and/or treatment of cancer.

Another aspect of the present invention relates to antibodies and other binders that specifically bind to a polypeptide of the instant invention. Accordingly antibodies or binders of the present invention specifically bind to OSPs, muteins, fusion proteins, and/or homologous proteins or polypeptides encoded by allelic variants of an OSNA as provided herein.

Another aspect of the present invention relates to agonists and antagonists of the nucleic acid molecules and polypeptides of this invention. The agonists and antagonists of the instant invention may be used to treat ovarian cancer and non-cancerous disease states in ovarian and to produce engineered ovarian tissue.

Another aspect of the present invention relates to methods for using the nucleic acid molecules to detect or amplify nucleic acid molecules that have similar or identical nucleic acid sequences compared to the nucleic acid molecules described herein. Such methods are useful in identifying, diagnosing, monitoring, staging, imaging and treating ovarian cancer and non-cancerous disease states in ovarian. Such methods are also useful in identifying and/or monitoring ovarian tissue. In addition, measurement of levels of one or more of the nucleic acid molecules of this invention may be useful for diagnostics as

part of panel in combination with known other markers, particularly those described in the ovarian cancer background section above.

Another aspect of the present invention relates to use of the nucleic acid molecules of this invention in gene therapy, for producing transgenic animals and cells, and for producing engineered ovarian tissue for treatment and research.

Another aspect of the present invention relates to methods for detecting polypeptides this invention, preferably using antibodies thereto. Such methods are useful to identify, diagnose, monitor, stage, image and treat ovarian cancer and non-cancerous disease states in ovarian. In addition, measurement of levels of one or more of the polypeptides of this invention may be useful to identify, diagnose, monitor, stage, image ovarian cancer in combination with known other markers, particularly those described in the ovarian cancer background section above. The polypeptides of the present invention can also be used to identify and/or monitor ovarian tissue, and to produce engineered ovarian tissue.

Yet another aspect of the present invention relates to a computer readable means of storing the nucleic acid and amino acid sequences of the invention. The records of the computer readable means can be accessed for reading and displaying of sequences for comparison, alignment and ordering of the sequences of the invention to other sequences. In addition, the computer records regarding the nucleic acid and/or amino acid sequences and/or measurements of their levels may be used alone or in combination with other markers to diagnose ovarian related diseases.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Techniques

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various

general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. *See, e.g.*, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press (1989) and Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 3d ed., Cold Spring Harbor Press (2001); Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates (1992, and Supplements to 2000); Ausubel *et al.*, Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology – 4th Ed., Wiley & Sons (1999); Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1990); and Harlow and Lane, Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1999).

Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

A "nucleic acid molecule" of this invention refers to a polymeric form of nucleotides and includes both sense and antisense strands of RNA, cDNA, genomic DNA, and synthetic forms and mixed polymers of the above. A nucleotide refers to a ribonucleotide, deoxynucleotide or a modified form of either type of nucleotide. A "nucleic acid molecule" as used herein is synonymous with "nucleic acid" and "polynucleotide." The term "nucleic acid molecule" usually refers to a molecule of at least 10 bases in length, unless otherwise specified. The term includes single and double stranded forms of DNA. In addition, a polynucleotide may include either or both naturally occurring and modified nucleotides linked together by naturally occurring and/or non-naturally occurring nucleotide linkages.

Nucleotides are represented by single letter symbols in nucleic acid molecule sequences. The following table lists symbols identifying nucleotides or groups of nucleotides which may occupy the symbol position on a nucleic acid molecule. *See* Nomenclature Committee of the International Union of Biochemistry (NC-IUB),

Nomenclature for incompletely specified bases in nucleic acid sequences, Recommendations 1984., *Eur J Biochem.* 150(1):1-5 (1985).

Symbol	Meaning	Group/Origin of Designation	Complementary Symbol
a	a	Adenine	t/u
g	g	Guanine	c
c	c	Cytosine	g
t	t	Thymine	a
u	u	Uracil	a
r	g or a	puRine	y
y	t/u or c	pYrimidine	r
m	a or c	aMino	k
k	g or t/u	Keto	m
s	g or c	Strong interactions 3H-bonds	w
w	a or t/u	Weak interactions 2H-bonds	s
b	g or c or t/u	not a	v
d	a or g or t/u	not c	h
h	a or c or t/u	not g	d
v	a or g or c	not t, not u	b
n	a or g or c or t/u, unknown, or other	aNy	n

The nucleic acid molecules may be modified chemically or biochemically or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those of skill in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoramidates, carbamates, etc.), charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, etc.), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen, etc.), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids, etc.) The term "nucleic acid molecule" also includes any topological conformation, including single-stranded, double-stranded, partially duplexed, triplexed, hairpinned, circular and padlocked conformations. Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

A "gene" is defined as a nucleic acid molecule that comprises a nucleic acid sequence that encodes a polypeptide and the expression control sequences that surround

the nucleic acid sequence that encodes the polypeptide. For instance, a gene may comprise a promoter, one or more enhancers, a nucleic acid sequence that encodes a polypeptide, downstream regulatory sequences and, possibly, other nucleic acid sequences involved in regulation of the expression of an RNA. As is well known in the art, eukaryotic genes usually contain both exons and introns. The term "exon" refers to a nucleic acid sequence found in genomic DNA that is bioinformatically predicted and/or experimentally confirmed to contribute contiguous sequence to a mature mRNA transcript. The term "intron" refers to a nucleic acid sequence found in genomic DNA that is predicted and/or confirmed to not contribute to a mature mRNA transcript, but rather to be "spliced out" during processing of the transcript.

A nucleic acid molecule or polypeptide is "derived" from a particular species if the nucleic acid molecule or polypeptide has been isolated from the particular species, or if the nucleic acid molecule or polypeptide is homologous to a nucleic acid molecule or polypeptide isolated from a particular species.

An "isolated" or "substantially pure" nucleic acid or polynucleotide (*e.g.*, an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components that naturally accompany the native polynucleotide in its natural host cell, *e.g.*, ribosomes, polymerases, or genomic sequences with which it is naturally associated. The term embraces a nucleic acid or polynucleotide that (1) has been removed from its naturally occurring environment, (2) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (3) is operatively linked to a polynucleotide which it is not linked to in nature, (4) does not occur in nature as part of a larger sequence or (5) includes nucleotides or internucleoside bonds that are not found in nature. The term "isolated" or "substantially pure" also can be used in reference to recombinant or cloned DNA isolates, chemically synthesized polynucleotide analogs, or polynucleotide analogs that are biologically synthesized by heterologous systems. The term "isolated nucleic acid molecule" includes nucleic acid molecules that are integrated into a host cell chromosome at a heterologous site, recombinant fusions of a native fragment to a heterologous sequence, recombinant vectors present as episomes or as integrated into a host cell chromosome.

A "part" of a nucleic acid molecule refers to a nucleic acid molecule that comprises a partial contiguous sequence of at least 10 bases of the reference nucleic acid molecule. Preferably, a part comprises at least 15 to 20 bases of a reference nucleic acid

molecule. In theory, a nucleic acid sequence of 17 nucleotides is of sufficient length to occur at random less frequently than once in the three gigabase human genome, and thus to provide a nucleic acid probe that can uniquely identify the reference sequence in a nucleic acid mixture of genomic complexity. A preferred part is one that comprises a nucleic acid sequence that can encode at least 6 contiguous amino acid sequences (fragments of at least 18 nucleotides) because they are useful in directing the expression or synthesis of peptides that are useful in mapping the epitopes of the polypeptide encoded by the reference nucleic acid. *See, e.g.*, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1984); and U.S. Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. A part may also comprise at least 25, 30, 35 or 40 nucleotides of a reference nucleic acid molecule, or at least 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides of a reference nucleic acid molecule. A part of a nucleic acid molecule may comprise no other nucleic acid sequences. Alternatively, a part of a nucleic acid may comprise other nucleic acid sequences from other nucleic acid molecules.

The term "oligonucleotide" refers to a nucleic acid molecule generally comprising a length of 200 bases or fewer. The term often refers to single-stranded deoxyribonucleotides, but it can refer as well to single-or double-stranded ribonucleotides, RNA:DNA hybrids and double-stranded DNAs, among others. Preferably, oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19 or 20 bases in length. Other preferred oligonucleotides are 25, 30, 35, 40, 45, 50, 55 or 60 bases in length. Oligonucleotides may be single-stranded, *e.g.* for use as probes or primers, or may be double-stranded, *e.g.* for use in the construction of a mutant gene. Oligonucleotides of the invention can be either sense or antisense oligonucleotides. An oligonucleotide can be derivatized or modified as discussed above for nucleic acid molecules.

Oligonucleotides, such as single-stranded DNA probe oligonucleotides, often are synthesized by chemical methods, such as those implemented on automated oligonucleotide synthesizers. However, oligonucleotides can be made by a variety of other methods, including in vitro recombinant DNA-mediated techniques and by expression of DNAs in cells and organisms. Initially, chemically synthesized DNAs typically are obtained without a 5' phosphate. The 5' ends of such oligonucleotides are not substrates for phosphodiester bond formation by ligation reactions that employ DNA

ligases typically used to form recombinant DNA molecules. Where ligation of such oligonucleotides is desired, a phosphate can be added by standard techniques, such as those that employ a kinase and ATP. The 3' end of a chemically synthesized oligonucleotide generally has a free hydroxyl group and, in the presence of a ligase, such as T4 DNA ligase, readily will form a phosphodiester bond with a 5' phosphate of another polynucleotide, such as another oligonucleotide. As is well known, this reaction can be prevented selectively, where desired, by removing the 5' phosphates of the other polynucleotide(s) prior to ligation.

The term "naturally occurring nucleotide" referred to herein includes naturally occurring deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "nucleotide linkages" referred to herein includes nucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate, phosphoroamidate, and the like. *See e.g.*, LaPlanche *et al. Nucl. Acids Res.* 14:9081-9093 (1986); Stein *et al. Nucl. Acids Res.* 16:3209-3221 (1988); Zon *et al. Anti-Cancer Drug Design* 6:539-568 (1991); Zon *et al.*, in Eckstein (ed.) Oligonucleotides and Analogues: A Practical Approach, pp. 87-108, Oxford University Press (1991); Uhlmann and Peyman *Chemical Reviews* 90:543 (1990), and U.S. Patent No. 5,151,510, the disclosure of which is hereby incorporated by reference in its entirety.

Unless specified otherwise, the left hand end of a polynucleotide sequence in sense orientation is the 5' end and the right hand end of the sequence is the 3' end. In addition, the left hand direction of a polynucleotide sequence in sense orientation is referred to as the 5' direction, while the right hand direction of the polynucleotide sequence is referred to as the 3' direction. Further, unless otherwise indicated, each nucleotide sequence is set forth herein as a sequence of deoxyribonucleotides. It is intended, however, that the given sequence be interpreted as would be appropriate to the polynucleotide composition: for example, if the isolated nucleic acid is composed of RNA, the given sequence intends ribonucleotides, with uridine substituted for thymidine.

The term "allelic variant" refers to one of two or more alternative naturally occurring forms of a gene, wherein each gene possesses a unique nucleotide sequence. In a preferred embodiment, different alleles of a given gene have similar or identical biological properties.

The term "percent sequence identity" in the context of nucleic acid sequences refers to the residues in two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number of different algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using FASTA, Gap or Bestfit, which are programs in Wisconsin Package Version 10.0, Genetics Computer Group (GCG), Madison, Wisconsin. FASTA, which includes, *e.g.*, the programs FASTA2 and FASTA3, provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.* 183: 63-98 (1990); Pearson, *Methods Mol. Biol.* 132: 185-219 (2000); Pearson, *Methods Enzymol.* 266: 227-258 (1996); Pearson, *J. Mol. Biol.* 276: 71-84 (1998)). Unless otherwise specified, default parameters for a particular program or algorithm are used. For instance, percent sequence identity between nucleic acid sequences can be determined using FASTA with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) or using Gap with its default parameters as provided in GCG Version 6.1.

A reference to a nucleic acid sequence encompasses its complement unless otherwise specified. Thus, a reference to a nucleic acid molecule having a particular sequence should be understood to encompass its complementary strand, with its complementary sequence. The complementary strand is also useful, *e.g.*, for antisense therapy, double stranded RNA (dsRNA) inhibition (RNAi), combination of triplex and antisense, hybridization probes and PCR primers.

In the molecular biology art, researchers use the terms "percent sequence identity", "percent sequence similarity" and "percent sequence homology" interchangeably. In this application, these terms shall have the same meaning with respect to nucleic acid sequences only.

The term "substantial similarity" or "substantial sequence similarity," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 50%, more preferably 60% of the nucleotide bases, usually at least about 70%, more usually at least

about 80%, preferably at least about 90%, and more preferably at least about 95-98% of the nucleotide bases, as measured by any well known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed above.

Alternatively, substantial similarity exists between a first and second nucleic acid sequence when the first nucleic acid sequence or fragment thereof hybridizes to an antisense strand of the second nucleic acid, under selective hybridization conditions. Typically, selective hybridization will occur between the first nucleic acid sequence and an antisense strand of the second nucleic acid sequence when there is at least about 55% sequence identity between the first and second nucleic acid sequences— preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90% — over a stretch of at least about 14 nucleotides, more preferably at least 17 nucleotides, even more preferably at least 20, 25, 30, 35, 40, 50, 60, 70, 80, 90 or 100 nucleotides.

Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, solvents, the base composition of the hybridizing species, length of the complementary regions, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. "Stringent hybridization conditions" and "stringent wash conditions" in the context of nucleic acid hybridization experiments depend upon a number of different physical parameters. The most important parameters include temperature of hybridization, base composition of the nucleic acids, salt concentration and length of the nucleic acid. One having ordinary skill in the art knows how to vary these parameters to achieve a particular stringency of hybridization. In general, "stringent hybridization" is performed at about 25°C below the thermal melting point (T_m) for the specific DNA hybrid under a particular set of conditions. "Stringent washing" is performed at temperatures about 5°C lower than the T_m for the specific DNA hybrid under a particular set of conditions. The T_m is the temperature at which 50% of the target sequence hybridizes to a perfectly matched probe. *See* Sambrook (1989), *supra*, p. 9.51.

The T_m for a particular DNA-DNA hybrid can be estimated by the formula:

$T_m = 81.5°C + 16.6 (\log_{10}[Na^+]) + 0.41$ (fraction G + C) –

0.63 (% formamide) - (600/l) where l is the length of the hybrid in base pairs.

The T_m for a particular RNA-RNA hybrid can be estimated by the formula:

$T_m = 79.8°C + 18.5 (\log_{10}[Na^+]) + 0.58$ (fraction G + C) +

11.8 (fraction G + C)^2 - 0.35 (% formamide) - (820/l).

The T_m for a particular RNA-DNA hybrid can be estimated by the formula:

$T_m = 79.8°C + 18.5(\log_{10}[Na^+]) + 0.58$ (fraction G + C) +

11.8 (fraction G + C)^2 - 0.50 (% formamide) - (820/l).

In general, the T_m decreases by 1-1.5°C for each 1% of mismatch between two nucleic acid sequences. Thus, one having ordinary skill in the art can alter hybridization and/or washing conditions to obtain sequences that have higher or lower degrees of sequence identity to the target nucleic acid. For instance, to obtain hybridizing nucleic acids that contain up to 10% mismatch from the target nucleic acid sequence, 10-15°C would be subtracted from the calculated T_m of a perfectly matched hybrid, and then the hybridization and washing temperatures adjusted accordingly. Probe sequences may also hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well known in the art.

An example of stringent hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100 complementary residues on a filter in a Southern or Northern blot or for screening a library is 50% formamide/6X SSC at 42°C for at least ten hours and preferably overnight (approximately 16 hours). Another example of stringent hybridization conditions is 6X SSC at 68°C without formamide for at least ten hours and preferably overnight. An example of moderate stringency hybridization conditions is 6X SSC at 55°C without formamide for at least ten hours and preferably overnight. An example of low stringency hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100 complementary residues on a filter in a Southern or northern blot or for screening a library is 6X SSC at 42°C for at least ten hours. Hybridization conditions to identify nucleic acid sequences that are similar but not identical can be identified by experimentally changing the hybridization temperature from 68°C to 42°C while keeping the salt concentration constant (6X SSC), or keeping the hybridization temperature and salt concentration constant (*e.g.* 42°C and 6X SSC) and varying the formamide concentration from 50% to 0%. Hybridization buffers may also include blocking agents to lower background. These agents are well known in the art. *See* Sambrook *et al.* (1989), *supra*, pages 8.46 and 9.46-9.58. *See also* Ausubel (1992), *supra*, Ausubel (1999), *supra*, and Sambrook (2001), *supra*.

Wash conditions also can be altered to change stringency conditions. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (*see* Sambrook (1989), *supra*, for SSC buffer). Often the high stringency wash is preceded by a low stringency wash to remove excess probe. An exemplary medium stringency wash for duplex DNA of more than 100 base pairs is 1x SSC at 45°C for 15 minutes. An exemplary low stringency wash for such a duplex is 4x SSC at 40°C for 15 minutes. In general, signal-to-noise ratio of 2x or higher than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization.

As defined herein, nucleic acids that do not hybridize to each other under stringent conditions are still substantially similar to one another if they encode polypeptides that are substantially identical to each other. This occurs, for example, when a nucleic acid is created synthetically or recombinantly using a high codon degeneracy as permitted by the redundancy of the genetic code.

Hybridization conditions for nucleic acid molecules that are shorter than 100 nucleotides in length (*e.g.*, for oligonucleotide probes) may be calculated by the formula:

$T_m = 81.5°C + 16.6(\log_{10}[Na^+]) + 0.41(\text{fraction G+C}) - (600/N)$, wherein N is change length and the $[Na^+]$ is 1 M or less. *See* Sambrook (1989), *supra*, p. 11.46. For hybridization of probes shorter than 100 nucleotides, hybridization is usually performed under stringent conditions (5-10°C below the T_m) using high concentrations (0.1-1.0 pmol/ml) of probe. *Id.* at p. 11.45. Determination of hybridization using mismatched probes, pools of degenerate probes or "guessmers," as well as hybridization solutions and methods for empirically determining hybridization conditions are well known in the art. *See, e.g.*, Ausubel (1999), *supra*; Sambrook (1989), *supra*, pp. 11.45-11.57.

The term "digestion" or "digestion of DNA" refers to catalytic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The various restriction enzymes referred to herein are commercially available and their reaction conditions, cofactors and other requirements for use are known and routine to the skilled artisan. For analytical purposes, typically, 1 μg of plasmid or DNA fragment is digested with about 2 units of enzyme in about 20 μl of reaction buffer. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 μg of DNA are digested with 20 to 250 units of enzyme in proportionately larger volumes. Appropriate buffers and substrate amounts for particular restriction enzymes are described in standard laboratory manuals, such as those referenced below, and are specified by commercial

suppliers. Incubation times of about 1 hour at 37°C are ordinarily used, but conditions may vary in accordance with standard procedures, the supplier's instructions and the particulars of the reaction. After digestion, reactions may be analyzed, and fragments may be purified by electrophoresis through an agarose or polyacrylamide gel, using well known methods that are routine for those skilled in the art.

The term "ligation" refers to the process of forming phosphodiester bonds between two or more polynucleotides, which most often are double-stranded DNAs. Techniques for ligation are well known to the art and protocols for ligation are described in standard laboratory manuals and references, such as, *e.g.*, Sambrook (1989), *supra.*

Genome-derived "single exon probes," are probes that comprise at least part of an exon ("reference exon") and can hybridize detectably under high stringency conditions to transcript-derived nucleic acids that include the reference exon but do not hybridize detectably under high stringency conditions to nucleic acids that lack the reference exon. Single exon probes typically further comprise, contiguous to a first end of the exon portion, a first intronic and/or intergenic sequence that is identically contiguous to the exon in the genome, and may contain a second intronic and/or intergenic sequence that is identically contiguous to the exon in the genome. The minimum length of genome-derived single exon probes is defined by the requirement that the exonic portion be of sufficient length to hybridize under high stringency conditions to transcript-derived nucleic acids, as discussed above. The maximum length of genome-derived single exon probes is defined by the requirement that the probes contain portions of no more than one exon. The single exon probes may contain priming sequences not found in contiguity with the rest of the probe sequence in the genome, which priming sequences are useful for PCR and other amplification-based technologies. In another aspect, the invention is directed to single exon probes based on the OSNAs disclosed herein.

In one embodiment, the term "microarray" refers to a "nucleic acid microarray" having a substrate-bound plurality of nucleic acids, hybridization to each of the plurality of bound nucleic acids being separately detectable. The substrate can be solid or porous, planar or non-planar, unitary or distributed. Nucleic acid microarrays include all the devices so called in Schena (ed.), DNA Microarrays: A Practical Approach (Practical Approach Series), Oxford University Press (1999); *Nature Genet.* 21(1)(suppl.):1 - 60 (1999); Schena (ed.), Microarray Biochip: Tools and Technology, Eaton Publishing Company/BioTechniques Books Division (2000). Additionally, these nucleic acid

microarrays include substrate-bound plurality of nucleic acids in which the plurality of nucleic acids are disposed on a plurality of beads, rather than on a unitary planar substrate, as is described, *inter alia*, in Brenner *et al.*, *Proc. Natl. Acad. Sci. USA* 97(4):1665-1670 (2000). Examples of nucleic acid microarrays may be found in U.S. Patent Nos. 6,391,623, 6,383,754, 6,383,749, 6,380,377, 6,379,897, 6,376,191, 6,372,431, 6,351,712 6,344,316, 6,316,193, 6,312,906, 6,309,828, 6,309,824, 6,306,643, 6,300,063, 6,287,850, 6,284,497, 6,284,465, 6,280,954, 6,262,216, 6,251,601, 6,245,518, 6,263,287, 6,251,601, 6,238,866, 6,228,575, 6,214,587, 6,203,989, 6,171,797, 6,103,474, 6,083,726, 6,054,274, 6,040,138, 6,083,726, 6,004,755, 6,001,309, 5,958,342, 5,952,180, 5,936,731, 5,843,655, 5,814,454, 5,837,196, 5,436,327, 5,412,087, 5,405,783, the disclosures of which are incorporated herein by reference in their entireties.

In an alternative embodiment, a "microarray" may also refer to a "peptide microarray" or "protein microarray" having a substrate-bound collection of plurality of polypeptides, the binding to each of the plurality of bound polypeptides being separately detectable. Alternatively, the peptide microarray ,may have a plurality of binders, including but not limited to monoclonal antibodies, polyclonal antibodies, phage display binders, yeast 2 hybrid binders, aptamers, which can specifically detect the binding of the polypeptides of this invention. The array may be based on autoantibody detection to the polypeptides of this invention, see Robinson *et al., Nature Medicine* 8(3):295-301 (2002). Examples of peptide arrays may be found in WO 02/31463, WO 02/25288, WO 01/94946, WO 01/88162, WO 01/68671, WO 01/57259, WO 00/61806, WO 00/54046, WO 00/47774, WO 99/40434, WO 99/39210, WO 97/42507 and U.S. Patent Nos. 6,268,210, 5,766,960, 5,143,854, the disclosures of which are incorporated herein by reference in their entireties.

In addition, determination of the levels of the OSNA or OSP may be made in a multiplex manner using techniques described in WO 02/29109, WO 02/24959, WO 01/83502, WO01/73113, WO 01/59432, WO 01/57269, WO 99/67641, the disclosures of which are incorporated herein by reference in their entireties.

The term "mutant", "mutated", or "mutation" when applied to nucleic acid sequences means that nucleotides in a nucleic acid sequence may be inserted, deleted or changed compared to a reference nucleic acid sequence. A single alteration may be made at a locus (a point mutation) or multiple nucleotides may be inserted, deleted or changed at a single locus. In addition, one or more alterations may be made at any number of loci

within a nucleic acid sequence. In a preferred embodiment of the present invention, the nucleic acid sequence is the wild type nucleic acid sequence encoding a OSP or is a OSNA. The nucleic acid sequence may be mutated by any method known in the art including those mutagenesis techniques described *infra*.

The term "error-prone PCR" refers to a process for performing PCR under conditions where the copying fidelity of the DNA polymerase is low, such that a high rate of point mutations is obtained along the entire length of the PCR product. *See, e.g.*, Leung *et al.*, *Technique* 1: 11-15 (1989) and Caldwell *et al.*, *PCR Methods Applic.* 2: 28-33 (1992).

The term "oligonucleotide-directed mutagenesis" refers to a process which enables the generation of site-specific mutations in any cloned DNA segment of interest. *See, e.g.* , Reidhaar-Olson *et al.*, *Science* 241: 53-57 (1988).

The term "assembly PCR" refers to a process which involves the assembly of a PCR product from a mixture of small DNA fragments. A large number of different PCR reactions occur in parallel in the same vial, with the products of one reaction priming the products of another reaction.

The term "sexual PCR mutagenesis" or "DNA shuffling" refers to a method of error-prone PCR coupled with forced homologous recombination between DNA molecules of different but highly related DNA sequence *in vitro*, caused by random fragmentation of the DNA molecule based on sequence similarity, followed by fixation of the crossover by primer extension in an error-prone PCR reaction. *See, e.g.*, Stemmer, *Proc. Natl. Acad. Sci. U.S.A.* 91: 10747-10751 (1994). DNA shuffling can be carried out between several related genes ("Family shuffling").

The term "*in vivo* mutagenesis" refers to a process of generating random mutations in any cloned DNA of interest which involves the propagation of the DNA in a strain of bacteria such as *E. coli* that carries mutations in one or more of the DNA repair pathways. These "mutator" strains have a higher random mutation rate than that of a wild-type parent. Propagating the DNA in a mutator strain will eventually generate random mutations within the DNA.

The term "cassette mutagenesis" refers to any process for replacing a small region of a double-stranded DNA molecule with a synthetic oligonucleotide "cassette" that differs from the native sequence. The oligonucleotide often contains completely and/or partially randomized native sequence.

The term "recursive ensemble mutagenesis" refers to an algorithm for protein engineering (protein mutagenesis) developed to produce diverse populations of phenotypically related mutants whose members differ in amino acid sequence. This method uses a feedback mechanism to control successive rounds of combinatorial cassette mutagenesis. *See, e.g.*, Arkin *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 89: 7811-7815 (1992).

The term "exponential ensemble mutagenesis" refers to a process for generating combinatorial libraries with a high percentage of unique and functional mutants, wherein small groups of residues are randomized in parallel to identify, at each altered position, amino acids which lead to functional proteins. *See, e.g.*, Delegrave *et al.*, *Biotechnology Research* 11: 1548-1552 (1993); Arnold, *Current Opinion in Biotechnology* 4: 450-455 (1993).

"Operatively linked" expression control sequences refers to a linkage in which the expression control sequence is either contiguous with the gene of interest to control the gene of interest, or acts in *trans* or at a distance to control the gene of interest.

The term "expression control sequence" as used herein refers to polynucleotide sequences which are necessary to affect the expression of coding sequences to which they are operatively linked. Expression control sequences are sequences which control the transcription, post-transcriptional events and translation of nucleic acid sequences. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (*e.g.*, ribosome binding sites); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

The term "vector," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Other vectors include cosmids, bacterial

artificial chromosomes (BAC) and yeast artificial chromosomes (YAC). Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Viral vectors that infect bacterial cells are referred to as bacteriophages. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication). Other vectors can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include other forms of expression vectors that serve equivalent functions.

The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

As used herein, the phrase "open reading frame" and the equivalent acronym "ORF" refers to that portion of a transcript-derived nucleic acid that can be translated in its entirety into a sequence of contiguous amino acids. As so defined, an ORF has length, measured in nucleotides, exactly divisible by 3. As so defined, an ORF need not encode the entirety of a natural protein.

As used herein, the phrase "ORF-encoded peptide" refers to the predicted or actual translation of an ORF.

As used herein, the phrase "degenerate variant" of a reference nucleic acid sequence is meant to be inclusive of all nucleic acid sequences that can be directly translated, using the standard genetic code, to provide an amino acid sequence identical to that translated from the reference nucleic acid sequence.

The term "polypeptide" encompasses both naturally occurring and non-naturally occurring proteins and polypeptides, as well as polypeptide fragments and polypeptide mutants, derivatives and analogs thereof. A polypeptide may be monomeric or polymeric. Further, a polypeptide may comprise a number of different modules within a single polypeptide each of which has one or more distinct activities. A preferred polypeptide in accordance with the invention comprises a OSP encoded by a nucleic acid molecule of the instant invention, or a fragment, mutant, analog and derivative thereof.

The term "isolated protein" or "isolated polypeptide" is a protein or polypeptide that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is free of other proteins from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A polypeptide or protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

A protein or polypeptide is "substantially pure," "substantially homogeneous" or "substantially purified" when at least about 60% to 75% of a sample exhibits a single species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A substantially pure polypeptide or protein will typically comprise about 50%, 60%, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be determined by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel with a stain well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

The term "fragment" when used herein with respect to polypeptides of the present invention refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion compared to a full-length OSP. In a preferred embodiment, the fragment is a contiguous sequence in which the amino acid sequence of the fragment is identical to the corresponding positions in the naturally occurring polypeptide. Fragments typically are at least 5, 6, 7, 8, 9 or 10 amino acids long, preferably at least 12, 14, 16 or 18 amino acids long, more preferably at least 20 amino acids long, more preferably at least 25, 30, 35, 40

or 45, amino acids, even more preferably at least 50 or 60 amino acids long, and even more preferably at least 70 amino acids long.

A "derivative" when used herein with respect to polypeptides of the present invention refers to a polypeptide which is substantially similar in primary structural sequence to a OSP but which include, *e.g.*, *in vivo* or *in vitro* chemical and biochemical modifications that are not found in the OSP. Such modifications include, for example, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Other modification include, *e.g.*, labeling with radionuclides, and various enzymatic modifications, as will be readily appreciated by those skilled in the art. A variety of methods for labeling polypeptides and of substituents or labels useful for such purposes are well known in the art, and include radioactive isotopes such as ^{125}I, ^{32}P, ^{35}S, ^{14}C and ^{3}H, ligands which bind to labeled antiligands (*e.g.*, antibodies), fluorophores, chemiluminescent agents, enzymes, and antiligands which can serve as specific binding pair members for a labeled ligand. The choice of label depends on the sensitivity required, ease of conjugation with the primer, stability requirements, and available instrumentation. Methods for labeling polypeptides are well known in the art. *See* Ausubel (1992), *supra*; Ausubel (1999), *supra*.

The term "fusion protein" refers to polypeptides of the present invention coupled to a heterologous amino acid sequences. Fusion proteins are useful because they can be constructed to contain two or more desired functional elements from two or more different proteins. A fusion protein comprises at least 10 contiguous amino acids from a polypeptide of interest, more preferably at least 20 or 30 amino acids, even more preferably at least 40, 50 or 60 amino acids, yet more preferably at least 75, 100 or 125 amino acids. Fusion proteins can be produced recombinantly by constructing a nucleic acid sequence that encodes the polypeptide or a fragment thereof in frame with a nucleic

acid sequence encoding a different protein or peptide and then expressing the fusion protein. Alternatively, a fusion protein can be produced chemically by crosslinking the polypeptide or a fragment thereof to another protein.

The term "analog" refers to both polypeptide analogs and non-peptide analogs. The term "polypeptide analog" as used herein refers to a polypeptide that is comprised of a segment of at least 25 amino acids that has substantial identity to a portion of an amino acid sequence but which contains non-natural amino acids or non-natural inter-residue bonds. In a preferred embodiment, the analog has the same or similar biological activity as the native polypeptide. Typically, polypeptide analogs comprise a conservative amino acid substitution (or insertion or deletion) with respect to the naturally occurring sequence. Analogs typically are at least 20 amino acids long, preferably at least 50 amino acids long or longer, and can often be as long as a full-length naturally occurring polypeptide.

The term "non-peptide analog" refers to a compound with properties that are analogous to those of a reference polypeptide. A non-peptide compound may also be termed a "peptide mimetic" or a "peptidomimetic." Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to useful peptides may be used to produce an equivalent effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that has a desired biochemical property or pharmacological activity), but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH_2NH--, --CH_2S--, --CH_2-CH_2--, --CH=CH--(cis and trans), --$COCH_2$--, --$CH(OH)CH_2$--, and –CH_2SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo *et al., Ann. Rev. Biochem.* 61:387-418 (1992)). For example, one may add internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

The term "mutant" or "mutein" when referring to a polypeptide of the present invention relates to an amino acid sequence containing substitutions, insertions or deletions of one or more amino acids compared to the amino acid sequence of a OSP. A

mutein may have one or more amino acid point substitutions, in which a single amino acid at a position has been changed to another amino acid, one or more insertions and/or deletions, in which one or more amino acids are inserted or deleted, respectively, in the sequence of the naturally occurring protein, and/or truncations of the amino acid sequence at either or both the amino or carboxy termini. Further, a mutein may have the same or different biological activity as the naturally occurring protein. For instance, a mutein may have an increased or decreased biological activity. A mutein has at least 50% sequence similarity to the wild type protein, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are muteins having 80%, 85% or 90% sequence similarity to a OSP. In an even more preferred embodiment, a mutein exhibits 95% sequence identity, even more preferably 97%, even more preferably 98% and even more preferably 99%. Sequence similarity may be measured by any common sequence analysis algorithm, such as GAP or BESTFIT or other variation Smith-Waterman alignment. *See*, T. F. Smith and M. S. Waterman, J. Mol. Biol. 147:195-197 (1981) and W.R. Pearson, Genomics 11:635-650 (1991).

Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinity or enzymatic activity, and (5) confer or modify other physicochemical or functional properties of such analogs. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. In a preferred embodiment, the amino acid substitutions are moderately conservative substitutions or conservative substitutions. In a more preferred embodiment, the amino acid substitutions are conservative substitutions. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (*e.g.*, a replacement amino acid should not tend to disrupt a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in Creighton (ed.), Proteins, Structures and Molecular Principles, W. H. Freeman and Company (1984); Branden *et al.* (ed.), Introduction to Protein Structure, Garland Publishing (1991); Thornton *et al.*, *Nature* 354:105-106 (1991).

As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. *See* Golub *et al.* (eds.), Immunology - A Synthesis 2nd Ed., Sinauer Associates (1991). Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α-, α-disubstituted amino acids, N-alkyl amino acids, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, s-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the lefthand direction is the amino terminal direction and the right hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

By "homology" or "homologous" when referring to a polypeptide of the present invention it is meant polypeptides from different organisms with a similar sequence to the encoded amino acid sequence of a OSP and a similar biological activity or function. Although two polypeptides are said to be "homologous," this does not imply that there is necessarily an evolutionary relationship between the polypeptides. Instead, the term "homologous" is defined to mean that the two polypeptides have similar amino acid sequences and similar biological activities or functions. In a preferred embodiment, a homologous polypeptide is one that exhibits 50% sequence similarity to OSP, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are homologous polypeptides that exhibit 80%, 85% or 90% sequence similarity to a OSP. In a yet more preferred embodiment, a homologous polypeptide exhibits 95%, 97%, 98% or 99% sequence similarity.

When "sequence similarity" is used in reference to polypeptides, it is recognized that residue positions that are not identical often differ by conservative amino acid substitutions. In a preferred embodiment, a polypeptide that has "sequence similarity" comprises conservative or moderately conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (*e.g.*, charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative

substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. *See, e.g.*, Pearson, *Methods Mol. Biol.* 24: 307-31 (1994).

For instance, the following six groups each contain amino acids that are conservative substitutions for one another:

1) Serine (S), Threonine (T);
2) Aspartic Acid (D), Glutamic Acid (E);
3) Asparagine (N), Glutamine (Q);
4) Arginine (R), Lysine (K);
5) Isoleucine (I), Leucine (L), Methionine (M), Alanine (A), Valine (V), and
6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.*, *Science* 256: 1443-45 (1992). A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG contains programs such as "Gap" and "Bestfit" which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. *See, e.g.*, GCG Version 6.1. Other programs include FASTA, discussed *supra*.

A preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn. *See, e.g.,* Altschul *et al.*, *J. Mol. Biol.* 215: 403-410 (1990); Altschul *et al.*, *Nucleic Acids Res.* 25:3389-402 (1997). Preferred parameters for blastp are:

Expectation value:	10 (default)
Filter:	seg (default)
Cost to open a gap:	11 (default)

Cost to extend a gap: 1 (default
Max. alignments: 100 (default)
Word size: 11 (default)
No. of descriptions: 100 (default)
Penalty Matrix: BLOSUM62

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acid residues, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. When searching a database containing sequences from a large number of different organisms, it is preferable to compare amino acid sequences.

Algorithms other than blastp for database searching using amino acid sequences are known in the art. For instance, polypeptide sequences can be compared using FASTA, a program in GCG Version 6.1. FASTA (*e.g.*, FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (1990), *supra*; Pearson (2000), *supra*. For example, percent sequence identity between amino acid sequences can be determined using FASTA with its default or recommended parameters (a word size of 2 and the PAM250 scoring matrix), as provided in GCG Version 6.1.

An "antibody" refers to an intact immunoglobulin, or to an antigen-binding portion thereof that competes with the intact antibody for specific binding to a molecular species, *e.g.*, a polypeptide of the instant invention. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen-binding portions include, *inter alia*, Fab, Fab', $F(ab')_2$, Fv, dAb, and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. A Fab fragment is a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a $F(ab')_2$ fragment is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consists of the VH and CH1 domains; a Fv fragment consists of the VL and VH domains of a single arm of an antibody; and a dAb fragment consists of a VH domain. *See, e.g.,* Ward *et al.*, *Nature* 341: 544-546 (1989).

By "bind specifically" and "specific binding" as used herein it is meant the ability of the antibody to bind to a first molecular species in preference to binding to other

molecular species with which the antibody and first molecular species are admixed. An antibody is said specifically to "recognize" a first molecular species when it can bind specifically to that first molecular species.

A single-chain antibody (scFv) is an antibody in which VL and VH regions are paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain. *See, e.g.,* Bird *et al.*, *Science* 242: 423-426 (1988); Huston *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 5879-5883 (1988). Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites. *See e.g.*, Holliger *et al.*, *Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993); Poljak *et al.*, *Structure* 2: 1121-1123 (1994). One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an immunoadhesin. An immunoadhesin may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the immunoadhesin to specifically bind to a particular antigen of interest. A chimeric antibody is an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies.

An antibody may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For instance, a naturally occurring immunoglobulin has two identical binding sites, a single-chain antibody or Fab fragment has one binding site, while a "bispecific" or "bifunctional" antibody has two different binding sites.

An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. It is known that purified proteins, including purified antibodies, may be stabilized with non-naturally-associated components. The non-naturally-associated component may be a protein, such as albumin (*e.g.*, BSA) or a chemical such as polyethylene glycol (PEG).

A "neutralizing antibody" or "an inhibitory antibody" is an antibody that inhibits the activity of a polypeptide or blocks the binding of a polypeptide to a ligand that

normally binds to it. An "activating antibody" is an antibody that increases the activity of a polypeptide.

The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is less than1 μM, preferably less than100 nM and most preferably less than 10 nM.

The term "patient" includes human and veterinary subjects.

Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

The term "ovarian specific" refers to a nucleic acid molecule or polypeptide that is expressed predominantly in the ovarian as compared to other tissues in the body. In a preferred embodiment, a "ovarian specific" nucleic acid molecule or polypeptide is detected at a level that is 1.5-fold higher than any other tissue in the body. In a more preferred embodiment, the "ovarian specific" nucleic acid molecule or polypeptide is detected at a level that is 2-fold higher than any other tissue in the body, more preferably 5-fold higher, still more preferably at least 10-fold, 15-fold, 20-fold, 25-fold, 50-fold or 100-fold higher than any other tissue in the body. Nucleic acid molecule levels may be measured by nucleic acid hybridization, such as Northern blot hybridization, or quantitative PCR. Polypeptide levels may be measured by any method known to accurately quantitate protein levels, such as Western blot analysis.

Nucleic Acid Molecules, Regulatory Sequences, Vectors, Host Cells and Recombinant Methods of Making Polypeptides

Nucleic Acid Molecules

One aspect of the invention provides isolated nucleic acid molecules that are specific to the ovarian or to ovarian cells or tissue or that are derived from such nucleic acid molecules. These isolated ovarian specific nucleic acids (OSNAs) may comprise cDNA genomic DNA, RNA, or a combination thereof, a fragment of one of these nucleic acids, or may be a non-naturally occurring nucleic acid molecule. A OSNA may be

derived from an animal. In a preferred embodiment, the OSNA is derived from a human or other mammal. In a more preferred embodiment, the OSNA is derived from a human or other primate. In an even more preferred embodiment, the OSNA is derived from a human.

In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that is specific to ovarian, a ovarian-specific polypeptide (OSP). In a more preferred embodiment, the nucleic acid molecule encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 249-396. In another highly preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1-248. Nucleotide sequences of the instantly-described nucleic acid molecules were determined by assembling several DNA molecules from either public or proprietary databases. Some of the underlying DNA sequences are the result, directly or indirectly, of at least one enzymatic polymerization reaction (*e.g.*, reverse transcription and/or polymerase chain reaction) using an automated sequencer (such as the MegaBACE™ 1000, Amersham Biosciences, Sunnyvale, CA, USA).

Nucleic acid molecules of the present invention may also comprise sequences that selectively hybridizes to a nucleic acid molecule encoding a OSNA or a complement or antisense thereof. The hybridizing nucleic acid molecule may or may not encode a polypeptide or may or may not encode a OSP. However, in a preferred embodiment, the hybridizing nucleic acid molecule encodes a OSP. In a more preferred embodiment, the invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 249-396. In an even more preferred embodiment, the invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 1-248 or the antisense sequence thereof. Preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a OSP under low stringency conditions. More preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a OSP under moderate stringency conditions. Most preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a OSP under high stringency conditions. In a preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high

stringency conditions to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a polypeptide comprising an amino acid sequence of SEQ ID NO: 249-396. In a more preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule comprising a nucleic acid sequence selected from SEQ ID NO: 1-248.

Nucleic acid molecules of the present invention may also comprise nucleic acid sequences that exhibit substantial sequence similarity to a nucleic acid encoding a OSP or a complement of the encoding nucleic acid molecule. In this embodiment, it is preferred that the nucleic acid molecule exhibit substantial sequence similarity to a nucleic acid molecule encoding human OSP. More preferred is a nucleic acid molecule exhibiting substantial sequence similarity to a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 249-396. By substantial sequence similarity it is meant a nucleic acid molecule having at least 60% sequence identity with a nucleic acid molecule encoding a OSP, such as a polypeptide having an amino acid sequence of SEQ ID NO: 249-396, more preferably at least 70%, even more preferably at least 80% and even more preferably at least 85%. In a more preferred embodiment, the similar nucleic acid molecule is one that has at least 90% sequence identity with a nucleic acid molecule encoding a OSP, more preferably at least 95%, more preferably at least 97%, even more preferably at least 98%, and still more preferably at least 99%. Most preferred in this embodiment is a nucleic acid molecule that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a nucleic acid molecule encoding a OSP.

The nucleic acid molecules of the present invention are also inclusive of those exhibiting substantial sequence similarity to a OSNA or its complement. In this embodiment, it is preferred that the nucleic acid molecule exhibit substantial sequence similarity to a nucleic acid molecule having a nucleic acid sequence of SEQ ID NO: 1-248. By substantial sequence similarity it is meant a nucleic acid molecule that has at least 60% sequence identity with a OSNA, such as one having a nucleic acid sequence of SEQ ID NO: 1-248, more preferably at least 70%, even more preferably at least 80% and even more preferably at least 85%. More preferred is a nucleic acid molecule that has at least 90% sequence identity with a OSNA, more preferably at least 95%, more preferably at least 97%, even more preferably at least 98%, and still more preferably at least 99%.

Most preferred is a nucleic acid molecule that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a OSNA.

Nucleic acid molecules that exhibit substantial sequence similarity are inclusive of sequences that exhibit sequence identity over their entire length to a OSNA or to a nucleic acid molecule encoding a OSP, as well as sequences that are similar over only a part of its length. In this case, the part is at least 50 nucleotides of the OSNA or the nucleic acid molecule encoding a OSP, preferably at least 100 nucleotides, more preferably at least 150 or 200 nucleotides, even more preferably at least 250 or 300 nucleotides, still more preferably at least 400 or 500 nucleotides.

The substantially similar nucleic acid molecule may be a naturally occurring one that is derived from another species, especially one derived from another primate, wherein the similar nucleic acid molecule encodes an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 249-396 or demonstrates significant sequence identity to the nucleotide sequence of SEQ ID NO: 1-248. The similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule from a human, when the OSNA is a member of a gene family. The similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule derived from a non-primate, mammalian species, including without limitation, domesticated species, *e.g.*, dog, cat, mouse, rat, rabbit, hamster, cow, horse and pig; and wild animals, *e.g.*, monkey, fox, lions, tigers, bears, giraffes, zebras, etc. The substantially similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule derived from a non-mammalian species, such as birds or reptiles. The naturally occurring substantially similar nucleic acid molecule may be isolated directly from humans or other species. In another embodiment, the substantially similar nucleic acid molecule may be one that is experimentally produced by random mutation of a nucleic acid molecule. In another embodiment, the substantially similar nucleic acid molecule may be one that is experimentally produced by directed mutation of a OSNA. In a preferred embodiment, the substantially similar nucleic acid molecule is an OSNA.

The nucleic acid molecules of the present invention are also inclusive of allelic variants of a OSNA or a nucleic acid encoding a OSP. For example, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes and the sequence determined from one individual of a species may differ from other allelic forms present within the population. More than 1.4 million SNPs have already identified in the human

genome, International Human Genome Sequencing Consortium, *Nature* 409: 860-921 (2001) – Variants with small deletions and insertions of more than a single nucleotide are also found in the general population, and often do not alter the function of the protein. In addition, amino acid substitutions occur frequently among natural allelic variants, and often do not substantially change protein function.

In a preferred embodiment, the allelic variant is a variant of a gene, wherein the gene is transcribed into an mRNA that encodes a OSP. In a more preferred embodiment, the gene is transcribed into an mRNA that encodes a OSP comprising an amino acid sequence of SEQ ID NO: 249-396. In another preferred embodiment, the allelic variant is a variant of a gene, wherein the gene is transcribed into an mRNA that is a OSNA. In a more preferred embodiment, the gene is transcribed into an mRNA that comprises the nucleic acid sequence of SEQ ID NO: 1-248. Also preferred is that the allelic variant is a naturally occurring allelic variant in the species of interest, particularly human.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences comprising a part of a nucleic acid sequence of the instant invention. The part may or may not encode a polypeptide, and may or may not encode a polypeptide that is a OSP. In a preferred embodiment, the part encodes a OSP. In one embodiment, the nucleic acid molecule comprises a part of a OSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that hybridizes or exhibits substantial sequence similarity to a OSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that is an allelic variant of a OSNA. In yet another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that encodes a OSP. A part comprises at least 10 nucleotides, more preferably at least 15, 17, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides. The maximum size of a nucleic acid part is one nucleotide shorter than the sequence of the nucleic acid molecule encoding the full-length protein.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences that encode fusion proteins, homologous proteins, polypeptide fragments, muteins and polypeptide analogs, as described *infra*.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences containing modifications of the native nucleic acid molecule. Examples of such modifications include, but are not limited to, nonnative internucleoside bonds, post-synthetic modifications or altered nucleotide analogues. One having ordinary skill in the

art would recognize that the type of modification that may be made will depend upon the intended use of the nucleic acid molecule. For instance, when the nucleic acid molecule is used as a hybridization probe, the range of such modifications will be limited to those that permit sequence-discriminating base pairing of the resulting nucleic acid. When used to direct expression of RNA or protein *in vitro* or *in vivo*, the range of such modifications will be limited to those that permit the nucleic acid to function properly as a polymerization substrate. When the isolated nucleic acid is used as a therapeutic agent, the modifications will be limited to those that do not confer toxicity upon the isolated nucleic acid.

Accordingly, in one embodiment, a nucleic acid molecule may include nucleotide analogues that incorporate labels that are directly detectable, such as radiolabels or fluorophores, or nucleotide analogues that incorporate labels that can be visualized in a subsequent reaction, such as biotin or various haptens. The labeled nucleic acid molecules are particularly useful as hybridization probes.

Common radiolabeled analogues include those labeled with ^{33}P, ^{32}P, and ^{35}S, such as α-^{32}P-dATP, α-^{32}P-dCTP, α-^{32}P-dGTP, α-^{32}P-dTTP, α-^{32}P-3'dATP, α-^{32}P-ATP, α-^{32}P-CTP, α-^{32}P-GTP, α-^{32}P-UTP, α-^{35}S-dATP, γ-^{35}S-GTP, γ-^{33}P-dATP, and the like.

Commercially available fluorescent nucleotide analogues readily incorporated into the nucleic acids of the present invention include Cy3-dCTP, Cy3-dUTP, Cy5-dCTP, Cy3-dUTP (Amersham Biosciences, Piscataway, New Jersey, USA), fluorescein-12-dUTP, tetramethylrhodamine-6-dUTP, Texas Red®-5-dUTP, Cascade Blue®-7-dUTP, BODIPY® FL-14-dUTP, BODIPY® TMR-14-dUTP, BODIPY® TR-14-dUTP, Rhodamine Green™-5-dUTP, Oregon Green® 488-5-dUTP, Texas Red®-12-dUTP, BODIPY® 630/650-14-dUTP, BODIPY® 650/665-14-dUTP, Alexa Fluor® 488-5-dUTP, Alexa Fluor® 532-5-dUTP, Alexa Fluor® 568-5-dUTP, Alexa Fluor® 594-5-dUTP, Alexa Fluor® 546-14-dUTP, fluorescein-12-UTP, tetramethylrhodamine-6-UTP, Texas Red®-5-UTP, Cascade Blue®-7-UTP, BODIPY® FL-14-UTP, BODIPY® TMR-14-UTP, BODIPY® TR-14-UTP, Rhodamine Green™-5-UTP, Alexa Fluor® 488-5-UTP, Alexa Fluor® 546-14-UTP (Molecular Probes, Inc. Eugene, OR, USA). One may also custom synthesize nucleotides having other fluorophores. *See* Henegariu *et al.*, *Nature Biotechnol.* 18: 345-348 (2000).

Haptens that are commonly conjugated to nucleotides for subsequent labeling include biotin (biotin-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA;

biotin-21-UTP, biotin-21-dUTP, Clontech Laboratories, Inc., Palo Alto, CA, USA), digoxigenin (DIG-11-dUTP, alkali labile, DIG-11-UTP, Roche Diagnostics Corp., Indianapolis, IN, USA), and dinitrophenyl (dinitrophenyl-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA).

Nucleic acid molecules of the present invention can be labeled by incorporation of labeled nucleotide analogues into the nucleic acid. Such analogues can be incorporated by enzymatic polymerization, such as by nick translation, random priming, polymerase chain reaction (PCR), terminal transferase tailing, and end-filling of overhangs, for DNA molecules, and *in vitro* transcription driven, *e.g.*, from phage promoters, such as T7, T3, and SP6, for RNA molecules. Commercial kits are readily available for each such labeling approach. Analogues can also be incorporated during automated solid phase chemical synthesis. Labels can also be incorporated after nucleic acid synthesis, with the 5' phosphate and 3' hydroxyl providing convenient sites for post-synthetic covalent attachment of detectable labels.

Other post-synthetic approaches also permit internal labeling of nucleic acids. For example, fluorophores can be attached using a cisplatin reagent that reacts with the N7 of guanine residues (and, to a lesser extent, adenine bases) in DNA, RNA, and Peptide Nucleic Acids (PNA) to provide a stable coordination complex between the nucleic acid and fluorophore label (Universal Linkage System) (available from Molecular Probes, Inc., Eugene, OR, USA and Amersham Pharmacia Biotech, Piscataway, NJ, USA); *see* Alers *et al.*, *Genes, Chromosomes & Cancer* 25: 301- 305 (1999); Jelsma *et al.*, *J. NIH Res.* 5: 82 (1994); Van Belkum *et al.*, *BioTechniques* 16: 148-153 (1994). Alternatively, nucleic acids can be labeled using a disulfide-containing linker (FastTag™ Reagent, Vector Laboratories, Inc., Burlingame, CA, USA) that is photo- or thermally coupled to the target nucleic acid using aryl azide chemistry; after reduction, a free thiol is available for coupling to a hapten, fluorophore, sugar, affinity ligand, or other marker.

One or more independent or interacting labels can be incorporated into the nucleic acid molecules of the present invention. For example, both a fluorophore and a moiety that in proximity thereto acts to quench fluorescence can be included to report specific hybridization through release of fluorescence quenching or to report exonucleotidic excision. *See, e.g.,* Tyagi *et al.*, *Nature Biotechnol.* 14: 303-308 (1996); Tyagi *et al.*, *Nature Biotechnol.* 16: 49-53 (1998); Sokol *et al.*, *Proc. Natl. Acad. Sci. USA* 95: 11538-11543 (1998); Kostrikis *et al.*, *Science* 279: 1228-1229 (1998); Marras *et al.*,

Genet. Anal. 14: 151-156 (1999); Holland *et al.*, *Proc. Natl. Acad. Sci. USA* 88: 7276-7280 (1991); Heid *et al.*, *Genome Res.* 6(10): 986-94 (1996); Kuimelis *et al.*, *Nucleic Acids Symp. Ser.* (37): 255-6 (1997); and U.S. Patent Nos. 5,846,726, 5,925,517, 5,925,517, 5,723,591 and 5,538,848, the disclosures of which are incorporated herein by reference in their entireties.

Nucleic acid molecules of the present invention may also be modified by altering one or more native phosphodiester internucleoside bonds to more nuclease-resistant, internucleoside bonds. *See* Hartmann *et al.* (eds.), Manual of Antisense Methodology: Perspectives in Antisense Science, Kluwer Law International (1999); Stein *et al.* (eds.), Applied Antisense Oligonucleotide Technology, Wiley-Liss (1998); Chadwick *et al.* (eds.), Oligonucleotides as Therapeutic Agents – Symposium No. 209, John Wiley & Son Ltd (1997). Such altered internucleoside bonds are often desired for techniques or for targeted gene correction, Gamper *et al.*, *Nucl. Acids Res.* 28(21): 4332-4339 (2000). For double stranded RNA inhibition which may utilize either natural ds RNA or ds RNA modified in its, sugar, phosphate or base, *see* Hannon, *Nature* 418(11): 244-251 (2002); Fire *et al.* in WO 99/32619; Tuschl *et al.* in US2002/0086356; Kruetzer *et al.* in WO 00/44895, the disclosures of which are incorporated herein by reference in their entirety;. For circular antisense, see Kool in U.S. Patent No. 5,426,180, the disclosure of which is incorporated herein by reference in its entirety.

Modified oligonucleotide backbones include, without limitation, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Representative U.S. Patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050, the disclosures of

which are incorporated herein by reference in their entireties. In a preferred embodiment, the modified internucleoside linkages may be used for antisense techniques.

Other modified oligonucleotide backbones do not include a phosphorus atom, but have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts. Representative U.S. patents that teach the preparation of the above backbones include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437 and 5,677,439; the disclosures of which are incorporated herein by reference in their entireties.

In other preferred nucleic acid molecules, both the sugar and the internucleoside linkage are replaced with novel groups, such as peptide nucleic acids (PNA). In PNA compounds, the phosphodiester backbone of the nucleic acid is replaced with an amide-containing backbone, in particular by repeating N-(2-aminoethyl) glycine units linked by amide bonds. Nucleobases are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone, typically by methylene carbonyl linkages. PNA can be synthesized using a modified peptide synthesis protocol. PNA oligomers can be synthesized by both Fmoc and tBoc methods. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference in its entirety. Automated PNA synthesis is readily achievable on commercial synthesizers (*see, e.g.*, "PNA User's Guide," Rev. 2, February 1998, Perseptive Biosystems Part No. 60138, Applied Biosystems, Inc., Foster City, CA). PNA molecules are advantageous for a number of reasons. First, because the PNA backbone is uncharged, PNA/DNA and PNA/RNA duplexes have a higher thermal stability than is found in DNA/DNA and

DNA/RNA duplexes. The Tm of a PNA/DNA or PNA/RNA duplex is generally 1°C higher per base pair than the Tm of the corresponding DNA/DNA or DNA/RNA duplex (in 100 mM NaCl). Second, PNA molecules can also form stable PNA/DNA complexes at low ionic strength, under conditions in which DNA/DNA duplex formation does not occur. Third, PNA also demonstrates greater specificity in binding to complementary DNA because a PNA/DNA mismatch is more destabilizing than DNA/DNA mismatch. A single mismatch in mixed a PNA/DNA 15-mer lowers the Tm by 8–20°C (15°C on average). In the corresponding DNA/DNA duplexes, a single mismatch lowers the Tm by 4–16°C (11°C on average). Because PNA probes can be significantly shorter than DNA probes, their specificity is greater. Fourth, PNA oligomers are resistant to degradation by enzymes, and the lifetime of these compounds is extended both *in vivo* and *in vitro* because nucleases and proteases do not recognize the PNA polyamide backbone with nucleobase sidechains. *See, e.g.*, Ray *et al.*, *FASEB J.* 14(9): 1041-60 (2000); Nielsen *et al.*, *Pharmacol Toxicol.* 86(1): 3-7 (2000); Larsen *et al.*, *Biochim Biophys Acta.* 1489(1): 159-66 (1999); Nielsen, *Curr. Opin. Struct. Biol.* 9(3): 353-7 (1999), and Nielsen, *Curr. Opin. Biotechnol.* 10(1): 71-5 (1999).

Nucleic acid molecules may be modified compared to their native structure throughout the length of the nucleic acid molecule or can be localized to discrete portions thereof. As an example of the latter, chimeric nucleic acids can be synthesized that have discrete DNA and RNA domains and that can be used for targeted gene repair and modified PCR reactions, as further described in, Misra *et al.*, *Biochem.* 37: 1917-1925 (1998); and Finn *et al.*, *Nucl. Acids Res.* 24: 3357-3363 (1996), and U.S. Patent Nos. 5,760,012 and 5,731,181, the disclosures of which are incorporated herein by reference in their entireties.

Unless otherwise specified, nucleic acid molecules of the present invention can include any topological conformation appropriate to the desired use; the term thus explicitly comprehends, among others, single-stranded, double-stranded, triplexed, quadruplexed, partially double-stranded, partially-triplexed, partially-quadruplexed, branched, hairpinned, circular, and padlocked conformations. Padlock conformations and their utilities are further described in Banér *et al.*, *Curr. Opin. Biotechnol.* 12: 11-15 (2001); Escude *et al.*, *Proc. Natl. Acad. Sci. USA* 14: 96(19):10603-7 (1999); and Nilsson *et al.*, *Science* 265(5181): 2085-8 (1994). Triplex and quadruplex conformations, and their utilities, are reviewed in Praseuth *et al.*, *Biochim. Biophys. Acta.* 1489(1): 181-206

(1999); Fox, *Curr. Med. Chem.* 7(1): 17-37 (2000); Kochetkova *et al.*, *Methods Mol. Biol.* 130: 189-201 (2000); Chan *et al.*, *J. Mol. Med.* 75(4): 267-82 (1997); Rowley *et al.*, *Mol Med* 5(10): 693-700 (1999); Kool, *Annu Rev Biophys Biomol Struct.* 25: 1-28 (1996).

Methods for Using Nucleic Acid Molecules as Probes and Primers

The isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize, and quantify hybridizing nucleic acids in, and isolate hybridizing nucleic acids from, both genomic and transcript-derived nucleic acid samples. When free in solution, such probes are typically, but not invariably, detectably labeled; bound to a substrate, as in a microarray, such probes are typically, but not invariably unlabeled.

In one embodiment, the isolated nucleic acid molecules of the present invention can be used as probes to detect and characterize gross alterations in the gene of a OSNA, such as deletions, insertions, translocations, and duplications of the OSNA genomic locus through fluorescence *in situ* hybridization (FISH) to chromosome spreads. *See, e.g.*, Andreeff *et al.* (eds.), Introduction to Fluorescence *In Situ* Hybridization: Principles and Clinical Applications, John Wiley & Sons (1999). The isolated nucleic acid molecules of the present invention can be used as probes to assess smaller genomic alterations using, *e.g.*, Southern blot detection of restriction fragment length polymorphisms. The isolated nucleic acid molecules of the present invention can be used as probes to isolate genomic clones that include a nucleic acid molecule of the present invention, which thereafter can be restriction mapped and sequenced to identify deletions, insertions, translocations, and substitutions (single nucleotide polymorphisms, SNPs) at the sequence level. Alternatively, detection techniques such as molecular beacons may be used, see Kostrikis *et al. Science* 279:1228-1229 (1998).

The isolated nucleic acid molecules of the present invention can be also be used as probes to detect, characterize, and quantify OSNA in, and isolate OSNA from, transcript-derived nucleic acid samples. In one embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by length, and quantify mRNA by Northern blot of total or poly-A^+- selected RNA samples. In another embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by location, and quantify mRNA by *in situ* hybridization to tissue sections. *See, e.g.*, Schwarchzacher *et al.*, In Situ

Hybridization, Springer-Verlag New York (2000). In another preferred embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to measure the representation of clones in a cDNA library or to isolate hybridizing nucleic acid molecules acids from cDNA libraries, permitting sequence level characterization of mRNAs that hybridize to OSNAs, including, without limitations, identification of deletions, insertions, substitutions, truncations, alternatively spliced forms and single nucleotide polymorphisms. In yet another preferred embodiment, the nucleic acid molecules of the instant invention may be used in microarrays.

All of the aforementioned probe techniques are well within the skill in the art, and are described at greater length in standard texts such as Sambrook (2001), *supra*; Ausubel (1999), *supra*; and Walker *et al.* (eds.), The Nucleic Acids Protocols Handbook, Humana Press (2000).

In another embodiment, a nucleic acid molecule of the invention may be used as a probe or primer to identify and/or amplify a second nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of the invention. In this embodiment, it is preferred that the probe or primer be derived from a nucleic acid molecule encoding a OSP. More preferably, the probe or primer is derived from a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 249-396. Also preferred are probes or primers derived from a OSNA. More preferred are probes or primers derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-248.

In general, a probe or primer is at least 10 nucleotides in length, more preferably at least 12, more preferably at least 14 and even more preferably at least 16 or 17 nucleotides in length. In an even more preferred embodiment, the probe or primer is at least 1 8 nucleotides in length, even more preferably at least 20 nucleotides and even more preferably at least 22 nucleotides in length. Primers and probes may also be longer in length. For instance, a probe or primer may be 25 nucleotides in length, or may be 30, 40 or 50 nucleotides in length. Methods of performing nucleic acid hybridization using oligonucleotide probes are well known in the art. *See, e.g.*, Sambrook *et al.*, 1989, *supra*, Chapter 11 and pp. 11.31-11.32 and 11.40-11.44, which describes radiolabeling of short probes, and pp. 11.45-11.53, which describe hybridization conditions for oligonucleotide probes, including specific conditions for probe hybridization (pp. 11.50-11.51).

Methods of performing primer-directed amplification are also well known in the art. Methods for performing the polymerase chain reaction (PCR) are compiled, *inter alia*, in McPherson, PCR Basics: From Background to Bench, Springer Verlag (2000); Innis *et al.* (eds.), PCR Applications: Protocols for Functional Genomics, Academic Press (1999); Gelfand *et al.* (eds.), PCR Strategies, Academic Press (1998); Newton *et al.*, PCR, Springer-Verlag New York (1997); Burke (ed.), PCR: Essential Techniques, John Wiley & Son Ltd (1996); White (ed.), PCR Cloning Protocols: From Molecular Cloning to Genetic Engineering, Vol. 67, Humana Press (1996); and McPherson *et al.* (eds.), PCR 2: A Practical Approach, Oxford University Press, Inc. (1995). Methods for performing RT-PCR are collected, *e.g.*, in Siebert *et al.* (eds.), Gene Cloning and Analysis by RT-PCR, Eaton Publishing Company/Bio Techniques Books Division, 1998; and Siebert (ed.), PCR Technique:RT-PCR, Eaton Publishing Company/ BioTechniques Books (1995).

PCR and hybridization methods may be used to identify and/or isolate nucleic acid molecules of the present invention including allelic variants, homologous nucleic acid molecules and fragments. PCR and hybridization methods may also be used to identify, amplify and/or isolate nucleic acid molecules of the present invention that encode homologous proteins, analogs, fusion protein or muteins of the invention. Nucleic acid primers as described herein can be used to prime amplification of nucleic acid molecules of the invention, using transcript-derived or genomic DNA as template.

These nucleic acid primers can also be used, for example, to prime single base extension (SBE) for SNP detection (*See, e.g.*, U.S. Pat. No. 6,004,744, the disclosure of which is incorporated herein by reference in its entirety).

Isothermal amplification approaches, such as rolling circle amplification, are also now well-described. *See, e.g.*, Schweitzer *et al.*, *Curr. Opin. Biotechnol.* 12(1): 21-7 (2001); international patent publications WO 97/19193 and WO 00/15779, and U.S. Patent Nos. 5,854,033 and 5,714,320, the disclosures of which are incorporated herein by reference in their entireties. Rolling circle amplification can be combined with other techniques to facilitate SNP detection. *See, e.g.*, Lizardi *et al.*, *Nature Genet.* 19(3): 225-32 (1998).

Nucleic acid molecules of the present invention may be bound to a substrate either covalently or noncovalently. The substrate can be porous or solid, planar or non-planar, unitary or distributed. The bound nucleic acid molecules may be used as hybridization

probes, and may be labeled or unlabeled. In a preferred embodiment, the bound nucleic acid molecules are unlabeled.

In one embodiment, the nucleic acid molecule of the present invention is bound to a porous substrate, *e.g.*, a membrane, typically comprising nitrocellulose, nylon, or positively charged derivatized nylon. The nucleic acid molecule of the present invention can be used to detect a hybridizing nucleic acid molecule that is present within a labeled nucleic acid sample, *e.g.*, a sample of transcript-derived nucleic acids. In another embodiment, the nucleic acid molecule is bound to a solid substrate, including, without limitation, glass, amorphous silicon, crystalline silicon or plastics. Examples of plastics include, without limitation, polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene, polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof. The solid substrate may be any shape, including rectangular, disk-like and spherical. In a preferred embodiment, the solid substrate is a microscope slide or slide-shaped substrate.

The nucleic acid molecule of the present invention can be attached covalently to a surface of the support substrate or applied to a derivatized surface in a chaotropic agent that facilitates denaturation and adherence by presumed noncovalent interactions, or some combination thereof. The nucleic acid molecule of the present invention can be bound to a substrate to which a plurality of other nucleic acids are concurrently bound, hybridization to each of the plurality of bound nucleic acids being separately detectable. At low density, *e.g.* on a porous membrane, these substrate-bound collections are typically denominated macroarrays; at higher density, typically on a solid support, such as glass, these substrate bound collections of plural nucleic acids are colloquially termed microarrays. As used herein, the term microarray includes arrays of all densities. It is, therefore, another aspect of the invention to provide microarrays that comprise one or more of the nucleic acid molecules of the present invention.

In yet another embodiment, the invention is directed to single exon probes based on the OSNAs disclosed herein.

Expression Vectors, Host Cells and Recombinant Methods of Producing Polypeptides

Another aspect of the present invention provides vectors that comprise one or more of the isolated nucleic acid molecules of the present invention, and host cells in which such vectors have been introduced.

The vectors can be used, *inter alia*, for propagating the nucleic acid molecules of the present invention in host cells (cloning vectors), for shuttling the nucleic acid molecules of the present invention between host cells derived from disparate organisms (shuttle vectors), for inserting the nucleic acid molecules of the present invention into host cell chromosomes (insertion vectors), for expressing sense or antisense RNA transcripts of the nucleic acid molecules of the present invention *in vitro* or within a host cell, and for expressing polypeptides encoded by the nucleic acid molecules of the present invention, alone or as fusion proteins with heterologous polypeptides (expression vectors). Vectors are by now well known in the art, and are described, *inter alia*, in Jones *et al.* (eds.), Vectors: Cloning Applications: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Jones *et al.* (eds.), Vectors: Expression Systems: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Gacesa *et al.*, Vectors: Essential Data, John Wiley & Sons Ltd. (1995); Cid-Arregui (eds.), Viral Vectors: Basic Science and Gene Therapy, Eaton Publishing Co. (2000); Sambrook (2001), *supra*; Ausubel (1999), *supra*. Furthermore, a variety of vectors are available commercially. Use of existing vectors and modifications thereof are well within the skill in the art. Thus, only basic features need be described here.

Nucleic acid sequences may be expressed by operatively linking them to an expression control sequence in an appropriate expression vector and employing that expression vector to transform an appropriate unicellular host. Expression control sequences are sequences that control the transcription, post-transcriptional events and translation of nucleic acid sequences. Such operative linking of a nucleic sequence of this invention to an expression control sequence, of course, includes, if not already part of the nucleic acid sequence, the provision of a translation initiation codon, ATG or GTG, in the correct reading frame upstream of the nucleic acid sequence.

A wide variety of host/expression vector combinations may be employed in expressing the nucleic acid sequences of this invention. Useful expression vectors, for example, may consist of segments of chromosomal, non-chromosomal and synthetic nucleic acid sequences.

In one embodiment, prokaryotic cells may be used with an appropriate vector. Prokaryotic host cells are often used for cloning and expression. In a preferred embodiment, prokaryotic host cells include *E. coli*, *Pseudomonas*, *Bacillus* and *Streptomyces*. In a preferred embodiment, bacterial host cells are used to express the nucleic acid molecules of the instant invention. Useful expression vectors for bacterial hosts include bacterial plasmids, such as those from *E. coli*, *Bacillus* or *Streptomyces*, including pBluescript, pGEX-2T, pUC vectors, col E1, pCR1, pBR322, pMB9 and their derivatives, wider host range plasmids, such as RP4, phage DNAs, *e.g.*, the numerous derivatives of phage lambda, *e.g.*, NM989, λGT10 and λGT11, and other phages, *e.g.*, M13 and filamentous single stranded phage DNA. Where *E. coli* is used as host, selectable markers are, analogously, chosen for selectivity in gram negative bacteria: *e.g.*, typical markers confer resistance to antibiotics, such as ampicillin, tetracycline, chloramphenicol, kanamycin, streptomycin and zeocin; auxotrophic markers can also be used.

In other embodiments, eukaryotic host cells, such as yeast, insect, mammalian or plant cells, may be used. Yeast cells, typically *S. cerevisiae*, are useful for eukaryotic genetic studies, due to the ease of targeting genetic changes by homologous recombination and the ability to easily complement genetic defects using recombinantly expressed proteins. Yeast cells are useful for identifying interacting protein components, *e.g.* through use of a two-hybrid system. In a preferred embodiment, yeast cells are useful for protein expression. Vectors of the present invention for use in yeast will typically, but not invariably, contain an origin of replication suitable for use in yeast and a selectable marker that is functional in yeast. Yeast vectors include Yeast Integrating plasmids (*e.g.*, YIp5) and Yeast Replicating plasmids (the YRp and YEp series plasmids), Yeast Centromere plasmids (the YCp series plasmids), Yeast Artificial Chromosomes (YACs) which are based on yeast linear plasmids, denoted YLp, pGPD-2, 2μ plasmids and derivatives thereof, and improved shuttle vectors such as those described in Gietz *et al.*, *Gene*, 74: 527-34 (1988) (YIplac, YEplac and YCplac). Selectable markers in yeast vectors include a variety of auxotrophic markers, the most common of which are (in *Saccharomyces cerevisiae*) URA3, HIS3, LEU2, TRP1 and LYS2, which complement specific auxotrophic mutations, such as ura3-52, his3-D1, leu2-D1, trp1-D1 and lys2-201.

Insect cells may be chosen for high efficiency protein expression. Where the host cells are from *Spodoptera frugiperda, e.g.*, Sf9 and Sf21 cell lines, and expreSSF™ cells

(Protein Sciences Corp., Meriden, CT, USA), the vector replicative strategy is typically based upon the baculovirus life cycle. Typically, baculovirus transfer vectors are used to replace the wild-type AcMNPV polyhedrin gene with a heterologous gene of interest. Sequences that flank the polyhedrin gene in the wild-type genome are positioned 5' and 3' of the expression cassette on the transfer vectors. Following co-transfection with AcMNPV DNA, a homologous recombination event occurs between these sequences resulting in a recombinant virus carrying the gene of interest and the polyhedrin or p10 promoter. Selection can be based upon visual screening for lacZ fusion activity.

The host cells may also be mammalian cells, which are particularly useful for expression of proteins intended as pharmaceutical agents, and for screening of potential agonists and antagonists of a protein or a physiological pathway. Mammalian vectors intended for autonomous extrachromosomal replication will typically include a viral origin, such as the SV40 origin (for replication in cell lines expressing the large T-antigen, such as COS1 and COS7 cells), the papillomavirus origin, or the EBV origin for long term episomal replication (for use, *e.g.*, in 293-EBNA cells, which constitutively express the EBV EBNA-1 gene product and adenovirus E1A). Vectors intended for integration, and thus replication as part of the mammalian chromosome, can, but need not, include an origin of replication functional in mammalian cells, such as the SV40 origin. Vectors based upon viruses, such as adenovirus, adeno-associated virus, vaccinia virus, and various mammalian retroviruses, will typically replicate according to the viral replicative strategy. Selectable markers for use in mammalian cells include, include but are not limited to, resistance to neomycin (G418), blasticidin, hygromycin and zeocin, and selection based upon the purine salvage pathway using HAT medium.

Expression in mammalian cells can be achieved using a variety of plasmids, including pSV2, pBC12BI, and p91023, as well as lytic virus vectors (*e.g.*, vaccinia virus, adeno virus, and baculovirus), episomal virus vectors (*e.g.*, bovine papillomavirus), and retroviral vectors (*e.g.*, murine retroviruses). Useful vectors for insect cells include baculoviral vectors and pVL 941.

Plant cells can also be used for expression, with the vector replicon typically derived from a plant virus (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) and selectable markers chosen for suitability in plants.

It is known that codon usage of different host cells may be different. For example, a plant cell and a human cell may exhibit a difference in codon preference for encoding a

particular amino acid. As a result, human mRNA may not be efficiently translated in a plant, bacteria or insect host cell. Therefore, another embodiment of this invention is directed to codon optimization. The codons of the nucleic acid molecules of the invention may be modified to resemble, as much as possible, genes naturally contained within the host cell without altering the amino acid sequence encoded by the nucleic acid molecule.

Any of a wide variety of expression control sequences may be used in these vectors to express the nucleic acid molecules of this invention. Such useful expression control sequences include the expression control sequences associated with structural genes of the foregoing expression vectors. Expression control sequences that control transcription include, *e.g.*, promoters, enhancers and transcription termination sites. Expression control sequences in eukaryotic cells that control post-transcriptional events include splice donor and acceptor sites and sequences that modify the half-life of the transcribed RNA, *e.g.*, sequences that direct poly(A) addition or binding sites for RNA-binding proteins. Expression control sequences that control translation include ribosome binding sites, sequences which direct targeted expression of the polypeptide to or within particular cellular compartments, and sequences in the 5' and 3' untranslated regions that modify the rate or efficiency of translation.

Examples of useful expression control sequences for a prokaryote, *e.g.*, *E. coli*, will include a promoter, often a phage promoter, such as phage lambda pL promoter, the trc promoter, a hybrid derived from the trp and lac promoters, the bacteriophage T7 promoter (in *E. coli* cells engineered to express the T7 polymerase), the TAC or TRC system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, and the araBAD operon. Prokaryotic expression vectors may further include transcription terminators, such as the aspA terminator, and elements that facilitate translation, such as a consensus ribosome binding site and translation termination codon, Schomer *et al.*, *Proc. Natl. Acad. Sci. USA* 83: 8506-8510 (1986).

Expression control sequences for yeast cells, typically *S. cerevisiae*, will include a yeast promoter, such as the CYC1 promoter, the GAL1 promoter, the GAL10 promoter, ADH1 promoter, the promoters of the yeast α-mating system, or the GPD promoter, and will typically have elements that facilitate transcription termination, such as the transcription termination signals from the CYC1 or ADH1 gene.

Expression vectors useful for expressing proteins in mammalian cells will include a promoter active in mammalian cells. These promoters include, but are not limited to,

those derived from mammalian viruses, such as the enhancer-promoter sequences from the immediate early gene of the human cytomegalovirus (CMV), the enhancer-promoter sequences from the Rous sarcoma virus long terminal repeat (RSV LTR), the enhancer-promoter from SV40 and the early and late promoters of adenovirus. Other expression control sequences include the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase. Other expression control sequences include those from the gene comprising the OSNA of interest. Often, expression is enhanced by incorporation of polyadenylation sites, such as the late SV40 polyadenylation site and the polyadenylation signal and transcription termination sequences from the bovine growth hormone (BGH) gene, and ribosome binding sites. Furthermore, vectors can include introns, such as intron II of rabbit β-globin gene and the SV40 splice elements.

Preferred nucleic acid vectors also include a selectable or amplifiable marker gene and means for amplifying the copy number of the gene of interest. Such marker genes are well known in the art. Nucleic acid vectors may also comprise stabilizing sequences (*e.g.*, ori- or ARS-like sequences and telomere-like sequences), or may alternatively be designed to favor directed or non-directed integration into the host cell genome. In a preferred embodiment, nucleic acid sequences of this invention are inserted in frame into an expression vector that allows a high level expression of an RNA which encodes a protein comprising the encoded nucleic acid sequence of interest. Nucleic acid cloning and sequencing methods are well known to those of skill in the art and are described in an assortment of laboratory manuals, including Sambrook (1989), *supra*, Sambrook (2000), *supra*; and Ausubel (1992), *supra*, Ausubel (1999), *supra*. Product information from manufacturers of biological, chemical and immunological reagents also provide useful information.

Expression vectors may be either constitutive or inducible. Inducible vectors include either naturally inducible promoters, such as the trc promoter, which is regulated by the lac operon, and the pL promoter, which is regulated by tryptophan, the MMTV-LTR promoter, which is inducible by dexamethasone, or can contain synthetic promoters and/or additional elements that confer inducible control on adjacent promoters. Examples of inducible synthetic promoters are the hybrid Plac/ara-1 promoter and the PLtetO-1 promoter. The PLtetO-1 promoter takes advantage of the high expression levels from the PL promoter of phage lambda, but replaces the lambda repressor sites with two copies of operator 2 of the Tn10 tetracycline resistance operon, causing this promoter to

be tightly repressed by the Tet repressor protein and induced in response to tetracycline (Tc) and Tc derivatives such as anhydrotetracycline. Vectors may also be inducible because they contain hormone response elements, such as the glucocorticoid response element (GRE) and the estrogen response element (ERE), which can confer hormone inducibility where vectors are used for expression in cells having the respective hormone receptors. To reduce background levels of expression, elements responsive to ecdysone, an insect hormone, can be used instead, with coexpression of the ecdysone receptor.

In one embodiment of the invention, expression vectors can be designed to fuse the expressed polypeptide to small protein tags that facilitate purification and/or visualization. Such tags include a polyhistidine tag that facilitates purification of the fusion protein by immobilized metal affinity chromatography, for example using NiNTA resin (Qiagen Inc., Valencia, CA, USA) or TALON™ resin (cobalt immobilized affinity chromatography medium, Clontech Labs, Palo Alto, CA, USA). The fusion protein can include a chitin-binding tag and self-excising intein, permitting chitin-based purification with self-removal of the fused tag (IMPACT™ system, New England Biolabs, Inc., Beverley, MA, USA). Alternatively, the fusion protein can include a calmodulin-binding peptide tag, permitting purification by calmodulin affinity resin (Stratagene, La Jolla, CA, USA), or a specifically excisable fragment of the biotin carboxylase carrier protein, permitting purification of *in vivo* biotinylated protein using an avidin resin and subsequent tag removal (Promega, Madison, WI, USA). As another useful alternative, the polypeptides of the present invention can be expressed as a fusion to glutathione-S-transferase, the affinity and specificity of binding to glutathione permitting purification using glutathione affinity resins, such as Glutathione-Superflow Resin (Clontech Laboratories, Palo Alto, CA, USA), with subsequent elution with free glutathione. Other tags include, for example, the Xpress epitope, detectable by anti-Xpress antibody (Invitrogen, Carlsbad, CA, USA), a myc tag, detectable by anti-myc tag antibody, the V5 epitope, detectable by anti-V5 antibody (Invitrogen, Carlsbad, CA, USA), FLAG® epitope, detectable by anti-FLAG® antibody (Stratagene, La Jolla, CA, USA), and the HA epitope, detectable by anti-HA antibody.

For secretion of expressed polypeptides, vectors can include appropriate sequences that encode secretion signals, such as leader peptides. For example, the pSecTag2 vectors (Invitrogen, Carlsbad, CA, USA) are 5.2 kb mammalian expression vectors that carry the

secretion signal from the V-J2-C region of the mouse Ig kappa-chain for efficient secretion of recombinant proteins from a variety of mammalian cell lines.

Expression vectors can also be designed to fuse proteins encoded by the heterologous nucleic acid insert to polypeptides that are larger than purification and/or identification tags. Useful protein fusions include those that permit display of the encoded protein on the surface of a phage or cell, fusions to intrinsically fluorescent proteins, such as those that have a green fluorescent protein (GFP)-like chromophore, fusions to the IgG Fc region, and fusions for use in two hybrid systems.

Vectors for phage display fuse the encoded polypeptide to, *e.g.*, the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13. *See* Barbas *et al.*, Phage Display: A Laboratory Manual, Cold Spring Harbor Laboratory Press (2001); Kay *et al.* (eds.), Phage Display of Peptides and Proteins: A Laboratory Manual, Academic Press, Inc., (1996); Abelson *et al.* (eds.), Combinatorial Chemistry (Methods in Enzymology, Vol. 267) Academic Press (1996). Vectors for yeast display, *e.g.* the pYD1 yeast display vector (Invitrogen, Carlsbad, CA, USA), use the α-agglutinin yeast adhesion receptor to display recombinant protein on the surface of *S. cerevisiae*. Vectors for mammalian display, *e.g.*, the pDisplay™ vector (Invitrogen, Carlsbad, CA, USA), target recombinant proteins using an N-terminal cell surface targeting signal and a C-terminal transmembrane anchoring domain of platelet derived growth factor receptor.

A wide variety of vectors now exist that fuse proteins encoded by heterologous nucleic acids to the chromophore of the substrate-independent, intrinsically fluorescent green fluorescent protein from *Aequorea victoria* ("GFP") and its variants. The GFP-like chromophore can be selected from GFP-like chromophores found in naturally occurring proteins, such as *A. victoria* GFP (GenBank accession number AAA27721), *Renilla reniformis* GFP, FP583 (GenBank accession no. AF168419) (DsRed), FP593 (AF272711), FP483 (AF168420), FP484 (AF168424), FP595 (AF246709), FP486 (AF168421), FP538 (AF168423), and FP506 (AF168422), and need include only so much of the native protein as is needed to retain the chromophore's intrinsic fluorescence. Methods for determining the minimal domain required for fluorescence are known in the art. *See* Li *et al.*, *J. Biol. Chem.* 272: 28545-28549 (1997). Alternatively, the GFP-like chromophore can be selected from GFP-like chromophores modified from those found in nature. The methods for engineering such modified GFP-like chromophores and testing them for fluorescence

activity, both alone and as part of protein fusions, are well known in the art. *See* Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Palm *et al.*, *Methods Enzymol.* 302: 378-394 (1999). A variety of such modified chromophores are now commercially available and can readily be used in the fusion proteins of the present invention. These include EGFP ("enhanced GFP"), EBFP ("enhanced blue fluorescent protein"), BFP2, EYFP ("enhanced yellow fluorescent protein"), ECFP ("enhanced cyan fluorescent protein") or Citrine. EGFP (*see, e.g,* Cormack *et al.*, *Gene* 173: 33–38 (1996); U.S. Patent Nos. 6,090,919 and 5,804,387, the disclosures of which are incorporated herein by reference in their entireties) is found on a variety of vectors, both plasmid and viral, which are available commercially (Clontech Labs, Palo Alto, CA, USA); EBFP is optimized for expression in mammalian cells whereas BFP2, which retains the original jellyfish codons, can be expressed in bacteria (*see, e.g,.* Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Cormack *et al.*, *Gene* 173: 33-38 (1996)). Vectors containing these blue-shifted variants are available from Clontech Labs (Palo Alto, CA, USA). Vectors containing EYFP, ECFP (*see, e.g.*, Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996); Miyawaki *et al.*, *Nature* 388: 882-887 (1997)) and Citrine (*see, e.g.*, Heikal *et al.*, *Proc. Natl. Acad. Sci. USA* 97: 11996-12001 (2000)) are also available from Clontech Labs. The GFP-like chromophore can also be drawn from other modified GFPs, including those described in U.S. Patent Nos. 6,124,128; 6,096,865; 6,090,919; 6,066,476; 6,054,321; 6,027,881; 5,968,750; 5,874,304; 5,804,387; 5,777,079; 5,741,668; and 5,625,048, the disclosures of which are incorporated herein by reference in their entireties. *See* also Conn (ed.), Green Fluorescent Protein (Methods in Enzymology, Vol. 302), Academic Press, Inc. (1999); Yang, *et al.*, *J Biol Chem*, 273: 8212-6 (1998); Bevis *et al.*, *Nature Biotechnology*, 20:83-7 (2002). The GFP-like chromophore of each of these GFP variants can usefully be included in the fusion proteins of the present invention.

Fusions to the IgG Fc region increase serum half-life of protein pharmaceutical products through interaction with the FcRn receptor (also denominated the FcRp receptor and the Brambell receptor, FcRb), further described in International Patent Application nos. WO 97/43316, WO 97/34631, WO 96/32478, WO 96/18412, the disclosures of which are incorporated herein by reference in their entireties.

For long-term, high-yield recombinant production of the polypeptides of the present invention, stable expression is preferred. Stable expression is readily achieved by integration into the host cell genome of vectors having selectable markers, followed by

selection of these integrants. Vectors such as pUB6/V5-His A, B, and C (Invitrogen, Carlsbad, CA, USA) are designed for high-level stable expression of heterologous proteins in a wide range of mammalian tissue types and cell lines. pUB6/V5-His uses the promoter/enhancer sequence from the human ubiquitin C gene to drive expression of recombinant proteins: expression levels in 293, CHO, and NIH3T3 cells are comparable to levels from the CMV and human EF-1a promoters. The bsd gene permits rapid selection of stably transfected mammalian cells with the potent antibiotic blasticidin.

Replication incompetent retroviral vectors, typically derived from Moloney murine leukemia virus, also are useful for creating stable transfectants having integrated provirus. The highly efficient transduction machinery of retroviruses, coupled with the availability of a variety of packaging cell lines such as RetroPack™ PT 67, EcoPack2™-293, AmphoPack-293, and GP2-293 cell lines (all available from Clontech Laboratories, Palo Alto, CA, USA) allow a wide host range to be infected with high efficiency; varying the multiplicity of infection readily adjusts the copy number of the integrated provirus.

Of course, not all vectors and expression control sequences will function equally well to express the nucleic acid molecules of this invention. Neither will all hosts function equally well with the same expression system. However, one of skill in the art may make a selection among these vectors, expression control sequences and hosts without undue experimentation and without departing from the scope of this invention. For example, in selecting a vector, the host must be considered because the vector must be replicated in it. The vector's copy number, the ability to control that copy number, the ability to control integration, if any, and the expression of any other proteins encoded by the vector, such as antibiotic or other selection markers, should also be considered. The present invention further includes host cells comprising the vectors of the present invention, either present episomally within the cell or integrated, in whole or in part, into the host cell chromosome. Among other considerations, some of which are described above, a host cell strain may be chosen for its ability to process the expressed polypeptide in the desired fashion. Such post-translational modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation, and it is an aspect of the present invention to provide OSPs with such post-translational modifications.

In selecting an expression control sequence, a variety of factors should also be considered. These include, for example, the relative strength of the sequence, its

controllability, and its compatibility with the nucleic acid molecules of this invention, particularly with regard to potential secondary structures. Unicellular hosts should be selected by consideration of their compatibility with the chosen vector, the toxicity of the product coded for by the nucleic acid sequences of this invention, their secretion characteristics, their ability to fold the polypeptide correctly, their fermentation or culture requirements, and the ease of purification from them of the products coded for by the nucleic acid molecules of this invention.

The recombinant nucleic acid molecules and more particularly, the expression vectors of this invention may be used to express the polypeptides of this invention as recombinant polypeptides in a heterologous host cell. The polypeptides of this invention may be full-length or less than full-length polypeptide fragments recombinantly expressed from the nucleic acid molecules according to this invention. Such polypeptides include analogs, derivatives and muteins that may or may not have biological activity.

Vectors of the present invention will also often include elements that permit *in vitro* transcription of RNA from the inserted heterologous nucleic acid. Such vectors typically include a phage promoter, such as that from T7, T3, or SP6, flanking the nucleic acid insert. Often two different such promoters flank the inserted nucleic acid, permitting separate *in vitro* production of both sense and antisense strands.

Transformation and other methods of introducing nucleic acids into a host cell (*e.g.*, conjugation, protoplast transformation or fusion, transfection, electroporation, liposome delivery, membrane fusion techniques, high velocity DNA-coated pellets, viral infection and protoplast fusion) can be accomplished by a variety of methods which are well known in the art (*See*, for instance, Ausubel, *supra*, and Sambrook *et al.*, *supra*). Bacterial, yeast, plant or mammalian cells are transformed or transfected with an expression vector, such as a plasmid, a cosmid, or the like, wherein the expression vector comprises the nucleic acid of interest. Alternatively, the cells may be infected by a viral expression vector comprising the nucleic acid of interest. Depending upon the host cell, vector, and method of transformation used, transient or stable expression of the polypeptide will be constitutive or inducible. One having ordinary skill in the art will be able to decide whether to express a polypeptide transiently or stably, and whether to express the protein constitutively or inducibly.

A wide variety of unicellular host cells are useful in expressing the DNA sequences of this invention. These hosts may include well known eukaryotic and

prokaryotic hosts, such as strains of, fungi, yeast, insect cells such as *Spodoptera frugiperda* (SF9), animal cells such as CHO, as well as plant cells in tissue culture. Representative examples of appropriate host cells include, but are not limited to, bacterial cells, such as *E. coli*, *Caulobacter crescentus*, *Streptomyces* species, and *Salmonella typhimurium*; yeast cells, such as *Saccharomyces cerevisiae, Schizosaccharomyces pombe*, *Pichia pastoris*, *Pichia methanolica*; insect cell lines, such as those from *Spodoptera frugiperda* — *e.g.*, Sf9 and Sf21 cell lines, and expresSF™ cells (Protein Sciences Corp., Meriden, CT, USA) — *Drosophila* S2 cells, and *Trichoplusia ni* High Five® Cells (Invitrogen, Carlsbad, CA, USA); and mammalian cells. Typical mammalian cells include BHK cells, BSC 1 cells, BSC 40 cells, BMT 10 cells, VERO cells, COS1 cells, COS7 cells, Chinese hamster ovary (CHO) cells, 3T3 cells, NIH 3T3 cells, 293 cells, HEPG2 cells, HeLa cells, L cells, MDCK cells, HEK293 cells, WI38 cells, murine ES cell lines (*e.g.*, from strains 129/SV, C57/BL6, DBA-1, 129/SVJ), K562 cells, Jurkat cells, and BW5147 cells. Other mammalian cell lines are well known and readily available from the American Type Culture Collection (ATCC) (Manassas, VA, USA) and the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository at the Coriell Cell Repositories (Camden, NJ, USA). Cells or cell lines derived from ovarian are particularly preferred because they may provide a more native post-translational processing. Particularly preferred are human ovarian cells.

Particular details of the transfection, expression and purification of recombinant proteins are well documented and are understood by those of skill in the art. Further details on the various technical aspects of each of the steps used in recombinant production of foreign genes in bacterial cell expression systems can be found in a number of texts and laboratory manuals in the art. *See, e.g.*, Ausubel (1992), *supra*, Ausubel (1999), *supra*, Sambrook (1989), *supra*, and Sambrook (2001), *supra*.

Methods for introducing the vectors and nucleic acid molecules of the present invention into the host cells are well known in the art; the choice of technique will depend primarily upon the specific vector to be introduced and the host cell chosen.

Nucleic acid molecules and vectors may be introduced into prokaryotes, such as *E. coli,* in a number of ways. For instance, phage lambda vectors will typically be packaged using a packaging extract (*e.g.*, Gigapack® packaging extract, Stratagene, La Jolla, CA, USA), and the packaged virus used to infect *E. coli.*

Plasmid vectors will typically be introduced into chemically competent or electrocompetent bacterial cells. *E. coli* cells can be rendered chemically competent by treatment, *e.g.*, with $CaCl_2$, or a solution of Mg^{2+}, Mn^{2+}, Ca^{2+}, Rb^+ or K^+, dimethyl sulfoxide, dithiothreitol, and hexamine cobalt (III), Hanahan, *J. Mol. Biol.* 166(4):557-80 (1983), and vectors introduced by heat shock. A wide variety of chemically competent strains are also available commercially (*e.g.*, Epicurian Coli® XL10-Gold® Ultracompetent Cells (Stratagene, La Jolla, CA, USA); DH5α competent cells (Clontech Laboratories, Palo Alto, CA, USA); and TOP10 Chemically Competent E. coli Kit (Invitrogen, Carlsbad, CA, USA)). Bacterial cells can be rendered electrocompetent to take up exogenous DNA by electroporation by various pre-pulse treatments; vectors are introduced by electroporation followed by subsequent outgrowth in selected media. An extensive series of protocols is provided by BioRad (Richmond, CA, USA).

Vectors can be introduced into yeast cells by spheroplasting, treatment with lithium salts, electroporation, or protoplast fusion. Spheroplasts are prepared by the action of hydrolytic enzymes such as a snail-gut extract, usually denoted Glusulase or Zymolyase, or an enzyme from *Arthrobacter luteus* to remove portions of the cell wall in the presence of osmotic stabilizers, typically 1 M sorbitol. DNA is added to the spheroplasts, and the mixture is co-precipitated with a solution of polyethylene glycol (PEG) and Ca^{2+}. Subsequently, the cells are resuspended in a solution of sorbitol, mixed with molten agar and then layered on the surface of a selective plate containing sorbitol.

For lithium-mediated transformation, yeast cells are treated with lithium acetate to permeabilize the cell wall, DNA is added and the cells are co-precipitated with PEG. The cells are exposed to a brief heat shock, washed free of PEG and lithium acetate, and subsequently spread on plates containing ordinary selective medium. Increased frequencies of transformation are obtained by using specially-prepared single-stranded carrier DNA and certain organic solvents. Schiestl *et al.*, *Curr. Genet.* 16(5-6): 339-46 (1989).

For electroporation, freshly-grown yeast cultures are typically washed, suspended in an osmotic protectant, such as sorbitol, mixed with DNA, and the cell suspension pulsed in an electroporation device. Subsequently, the cells are spread on the surface of plates containing selective media. Becker *et al.*, *Methods Enzymol.* 194: 182-187 (1991). The efficiency of transformation by electroporation can be increased over 100-fold by

using PEG, single-stranded carrier DNA and cells that are in late log-phase of growth. Larger constructs, such as YACs, can be introduced by protoplast fusion.

Mammalian and insect cells can be directly infected by packaged viral vectors, or transfected by chemical or electrical means. For chemical transfection, DNA can be coprecipitated with $CaPO_4$ or introduced using liposomal and nonliposomal lipid-based agents. Commercial kits are available for $CaPO_4$ transfection (CalPhos™ Mammalian Transfection Kit, Clontech Laboratories, Palo Alto, CA, USA), and lipid-mediated transfection can be practiced using commercial reagents, such as LIPOFECTAMINE™ 2000, LIPOFECTAMINE™ Reagent, CELLFECTIN® Reagent, and LIPOFECTIN® Reagent (Invitrogen, Carlsbad, CA, USA), DOTAP Liposomal Transfection Reagent, FuGENE 6, X-tremeGENE Q2, DOSPER, (Roche Molecular Biochemicals, Indianapolis, IN USA), Effectene™, PolyFect®, Superfect® (Qiagen, Inc., Valencia, CA, USA). Protocols for electroporating mammalian cells can be found in, for example, ; Norton *et al.* (eds.), Gene Transfer Methods: Introducing DNA into Living Cells and Organisms, BioTechniques Books, Eaton Publishing Co. (2000). Other transfection techniques include transfection by particle bombardment and microinjection. *See, e.g.*, Cheng *et al., Proc. Natl. Acad. Sci. USA* 90(10): 4455-9 (1993); Yang *et al., Proc. Natl. Acad. Sci. USA* 87(24): 9568-72 (1990).

Production of the recombinantly produced proteins of the present invention can optionally be followed by purification.

Purification of recombinantly expressed proteins is now well within the skill in the art and thus need not be detailed here. *See, e.g.*, Thorner *et al.* (eds.), Applications of Chimeric Genes and Hybrid Proteins, Part A: Gene Expression and Protein Purification (Methods in Enzymology, Vol. 326), Academic Press (2000); Harbin (ed.), Cloning, Gene Expression and Protein Purification : Experimental Procedures and Process Rationale, Oxford Univ. Press (2001); Marshak *et al.*, Strategies for Protein Purification and Characterization: A Laboratory Course Manual, Cold Spring Harbor Laboratory Press (1996); and Roe (ed.), Protein Purification Applications, Oxford University Press (2001).

Briefly, however, if purification tags have been fused through use of an expression vector that appends such tag, purification can be effected, at least in part, by means appropriate to the tag, such as use of immobilized metal affinity chromatography for polyhistidine tags. Other techniques common in the art include ammonium sulfate

fractionation, immunoprecipitation, fast protein liquid chromatography (FPLC), high performance liquid chromatography (HPLC), and preparative gel electrophoresis.

Polypeptides, including Fragments Muteins, Homologous Proteins, Allelic Variants, Analogs and Derivatives

Another aspect of the invention relates to polypeptides encoded by the nucleic acid molecules described herein. In a preferred embodiment, the polypeptide is a ovarian specific polypeptide (OSP). In an even more preferred embodiment, the polypeptide comprises an amino acid sequence of SEQ ID NO:249-396 or is derived from a polypeptide having the amino acid sequence of SEQ ID NO: 249-396. A polypeptide as defined herein may be produced recombinantly, as discussed *supra*, may be isolated from a cell that naturally expresses the protein, or may be chemically synthesized following the teachings of the specification and using methods well known to those having ordinary skill in the art.

Polypeptides of the present invention may also comprise a part or fragment of a OSP. In a preferred embodiment, the fragment is derived from a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 249-396. Polypeptides of the present invention comprising a part or fragment of an entire OSP may or may not be OSPs. For example, a full-length polypeptide may be ovarian-specific, while a fragment thereof may be found in other tissues as well as in ovarian. A polypeptide that is not a OSP, whether it is a fragment, analog, mutein, homologous protein or derivative, is nevertheless useful, especially for immunizing animals to prepare anti-OSP antibodies. In a preferred embodiment, the part or fragment is a OSP. Methods of determining whether a polypeptide of the present invention is a OSP are described *infra*.

Polypeptides of the present invention comprising fragments of at least 6 contiguous amino acids are also useful in mapping B cell and T cell epitopes of the reference protein. *See, e.g.*, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81: 3998-4002 (1984) and U.S. Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. Because the fragment need not itself be immunogenic, part of an immunodominant epitope, nor even recognized by native antibody, to be useful in such epitope mapping, all fragments of at least 6 amino acids of a polypeptide of the present invention have utility in such a study.

Polypeptides of the present invention comprising fragments of at least 8 contiguous amino acids, often at least 15 contiguous amino acids, are useful as immunogens for raising antibodies that recognize polypeptides of the present invention. *See, e.g.*, Lerner, Nature 299: 592-596 (1982); Shinnick *et al.*, *Annu. Rev. Microbiol.* 37: 425-46 (1983); Sutcliffe *et al.*, *Science* 219: 660-6 (1983). As further described in the above-cited references, virtually all 8-mers, conjugated to a carrier, such as a protein, prove immunogenic and are capable of eliciting antibody for the conjugated peptide; accordingly, all fragments of at least 8 amino acids of the polypeptides of the present invention have utility as immunogens.

Polypeptides comprising fragments of at least 8, 9, 10 or 12 contiguous amino acids are also useful as competitive inhibitors of binding of the entire polypeptide, or a portion thereof, to antibodies (as in epitope mapping), and to natural binding partners, such as subunits in a multimeric complex or to receptors or ligands of the subject protein; this competitive inhibition permits identification and separation of molecules that bind specifically to the polypeptide of interest. See U.S. Patent Nos. 5,539,084 and 5,783,674, incorporated herein by reference in their entireties.

The polypeptide of the present invention thus preferably is at least 6 amino acids in length, typically at least 8, 9, 10 or 12 amino acids in length, and often at least 15 amino acids in length. Often, the polypeptide of the present invention is at least 20 amino acids in length, even 25 amino acids, 30 amino acids, 35 amino acids, or 50 amino acids or more in length. Of course, larger polypeptides having at least 75 amino acids, 100 amino acids, or even 150 amino acids are also useful, and at times preferred.

One having ordinary skill in the art can produce fragments by truncating the nucleic acid molecule, *e.g.*, a OSNA, encoding the polypeptide and then expressing it recombinantly. Alternatively, one can produce a fragment by chemically synthesizing a portion of the full-length polypeptide. One may also produce a fragment by enzymatically cleaving either a recombinant polypeptide or an isolated naturally occurring polypeptide. Methods of producing polypeptide fragments are well known in the art. *See, e.g.*, Sambrook (1989), *supra;* Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. In one embodiment, a polypeptide comprising only a fragment, preferably a fragment of a OSP, may be produced by chemical or enzymatic cleavage of a OSP polypeptide. In a preferred embodiment, a polypeptide fragment is produced by

expressing a nucleic acid molecule of the present invention encoding a fragment, preferably of a OSP, in a host cell.

Polypeptides of the present invention are also inclusive of mutants, fusion proteins, homologous proteins and allelic variants.

A mutant protein, or mutein, may have the same or different properties compared to a naturally occurring polypeptide and comprises at least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of a native polypeptide. Small deletions and insertions can often be found that do not alter the function of a protein. Muteins may or may not be ovarian-specific. Preferably, the mutein is ovarian-specific. More preferably the mutein is a polypeptide that comprises at least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of SEQ ID NO: 249-396. Accordingly, in a preferred embodiment, the mutein is one that exhibits at least 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a OSP comprising an amino acid sequence of SEQ ID NO: 249-396. In a yet more preferred embodiment, the mutein exhibits at least 85%, more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97%, 98%, 99% or 99.5% sequence identity to a OSP comprising an amino acid sequence of SEQ ID NO: 249-396.

A mutein may be produced by isolation from a naturally occurring mutant cell, tissue or organism. A mutein may be produced by isolation from a cell, tissue or organism that has been experimentally mutagenized. Alternatively, a mutein may be produced by chemical manipulation of a polypeptide, such as by altering the amino acid residue to another amino acid residue using synthetic or semi-synthetic chemical techniques. In a preferred embodiment, a mutein is produced from a host cell comprising a mutated nucleic acid molecule compared to the naturally occurring nucleic acid molecule. For instance, one may produce a mutein of a polypeptide by introducing one or more mutations into a nucleic acid molecule of the invention and then expressing it recombinantly. These mutations may be targeted, in which particular encoded amino acids are altered, or may be untargeted, in which random encoded amino acids within the polypeptide are altered. Muteins with random amino acid alterations can be screened for a particular biological activity or property, particularly whether the polypeptide is ovarian-specific, as described below. Multiple random mutations can be introduced into the gene by methods well

known to the art, *e.g.*, by error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, *in vivo* mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis and site-specific mutagenesis. Methods of producing muteins with targeted or random amino acid alterations are well known in the art. *See, e.g.*, Sambrook (1989), *supra;* Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), as well as U.S. Patent No. 5,223,408, which is herein incorporated by reference in its entirety.

The invention also contemplates polypeptides that are homologous to a polypeptide of the invention. In a preferred embodiment, the polypeptide is homologous to a OSP. In an even more preferred embodiment, the polypeptide is homologous to a OSP selected from the group having an amino acid sequence of SEQ ID NO: 249-396. By homologous polypeptide it is means one that exhibits significant sequence identity to a OSP, preferably a OSP having an amino acid sequence of SEQ ID NO: 249-396. By significant sequence identity it is meant that the homologous polypeptide exhibits at least 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a OSP comprising an amino acid sequence of SEQ ID NO: 249-396. More preferred are homologous polypeptides exhibiting at least 85%, more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97% or 98% sequence identity to a OSP comprising an amino acid sequence of SEQ ID NO: 249-396. Most preferably, the homologous polypeptide exhibits at least 99%, more preferably 99.5%, even more preferably 99.6%, 99.7%, 99.8% or 99.9% sequence identity to a OSP comprising an amino acid sequence of SEQ ID NO: 249-396. In a preferred embodiment, the amino acid substitutions of the homologous polypeptide are conservative amino acid substitutions as discussed above.

Homologous polypeptides of the present invention also comprise polypeptide encoded by a nucleic acid molecule that selectively hybridizes to a OSNA or an antisense sequence thereof. In this embodiment, it is preferred that the homologous polypeptide be encoded by a nucleic acid molecule that hybridizes to a OSNA under low stringency, moderate stringency or high stringency conditions, as defined herein. More preferred is a homologous polypeptide encoded by a nucleic acid sequence which hybridizes to a OSNA selected from the group consisting of SEQ ID NO: 1-248 or a homologous polypeptide encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule that encodes

a OSP, preferably an OSP of SEQ ID NO:249-396 under low stringency, moderate stringency or high stringency conditions, as defined herein.

Homologous polypeptides of the present invention may be naturally occurring and derived from another species, especially one derived from another primate, such as chimpanzee, gorilla, rhesus macaque, or baboon, wherein the homologous polypeptide comprises an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 249-396. The homologous polypeptide may also be a naturally occurring polypeptide from a human, when the OSP is a member of a family of polypeptides. The homologous polypeptide may also be a naturally occurring polypeptide derived from a non-primate, mammalian species, including without limitation, domesticated species, *e.g.*, dog, cat, mouse, rat, rabbit, guinea pig, hamster, cow, horse, goat or pig. The homologous polypeptide may also be a naturally occurring polypeptide derived from a non-mammalian species, such as birds or reptiles. The naturally occurring homologous protein may be isolated directly from humans or other species. Alternatively, the nucleic acid molecule encoding the naturally occurring homologous polypeptide may be isolated and used to express the homologous polypeptide recombinantly. The homologous polypeptide may also be one that is experimentally produced by random mutation of a nucleic acid molecule and subsequent expression of the nucleic acid molecule. Alternatively, the homologous polypeptide may be one that is experimentally produced by directed mutation of one or more codons to alter the encoded amino acid of a OSP. In a preferred embodiment, the homologous polypeptide encodes a polypeptide that is a OSP.

Relatedness of proteins can also be characterized using a second functional test, the ability of a first protein competitively to inhibit the binding of a second protein to an antibody. It is, therefore, another aspect of the present invention to provide isolated polpeptide not only identical in sequence to those described with particularity herein, but also to provide isolated polypeptide ("cross-reactive proteins") that competitively inhibit the binding of antibodies to all or to a portion of various of the isolated polypeptides of the present invention. Such competitive inhibition can readily be determined using immunoassays well known in the art.

As discussed above, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes, and the sequence determined from one individual of a species may differ from other allelic forms present within the population. Thus, polypeptides of the present invention are also inclusive of those encoded by an allelic variant of a nucleic acid

molecule encoding a OSP. In this embodiment, it is preferred that the polypeptide be encoded by an allelic variant of a gene that encodes a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO: 249-396. More preferred is that the polypeptide be encoded by an allelic variant of a gene that has the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1-248.

Polypeptides of the present invention are also inclusive of derivative polypeptides encoded by a nucleic acid molecule according to the instant invention. In this embodiment, it is preferred that the polypeptide be a OSP. Also preferred are derivative polypeptides having an amino acid sequence selected from the group consisting of SEQ ID NO: 249-396 and which has been acetylated, carboxylated, phosphorylated, glycosylated, ubiquitinated or other PTMs. In another preferred embodiment, the derivative has been labeled with, *e.g.*, radioactive isotopes such as ^{125}I, ^{32}P, ^{35}S, and ^{3}H. In another preferred embodiment, the derivative has been labeled with fluorophores, chemiluminescent agents, enzymes, and antiligands that can serve as specific binding pair members for a labeled ligand.

Polypeptide modifications are well known to those of skill and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as, for instance Creighton, Protein Structure and Molecular Properties, 2nd ed., W. H. Freeman and Company (1993). Many detailed reviews are available on this subject, such as, for example, those provided by Wold, in Johnson (ed.), Posttranslational Covalent Modification of Proteins, pgs. 1-12, Academic Press (1983); Seifter *et al.*, *Meth. Enzymol.* 182: 626-646 (1990) and Rattan *et al.*, *Ann. N.Y. Acad. Sci.* 663: 48-62 (1992).

One may determine whether a polypeptide of the invention is likely to be post-translationally modified by analyzing the sequence of the polypeptide to determine if there are peptide motifs indicative of sites for post-translational modification. There are a number of computer programs that permit prediction of post-translational modifications. See, e.g., www.expasy.org (accessed November 11, 2002), which includes PSORT, for prediction of protein sorting signals and localization sites, SignalP, for prediction of signal peptide cleavage sites, MITOPROT and Predotar, for prediction of mitochondrial targeting sequences, NetOGlyc, for prediction of type O-glycosylation sites in mammalian proteins,

big-PI Predictor and DGPI, for prediction of prenylation-anchor and cleavage sites, and NetPhos, for prediction of Ser, Thr and Tyr phosphorylation sites in eukaryotic proteins. Other computer programs, such as those included in GCG, also may be used to determine post-translational modification peptide motifs.

General examples of types of post-translational modifications include, but are not limited to: (Z)-dehydrobutyrine; 1-chondroitin sulfate-L-aspartic acid ester; 1'-glycosyl-L-tryptophan; 1'-phospho-L-histidine; 1-thioglycine; 2'-(S-L-cysteinyl)-L-histidine; 2'-[3-carboxamido (trimethylammonio)propyl]-L-histidine; 2'-alpha-mannosyl-L-tryptophan; 2-methyl-L-glutamine; 2-oxobutanoic acid; 2-pyrrolidone carboxylic acid; 3'-(1'-L-histidyl)-L-tyrosine; 3'-(8alpha-FAD)-L-histidine; 3'-(S-L-cysteinyl)-L-tyrosine; 3', 3",5'-triiodo-L-thyronine; 3'-4'-phospho-L-tyrosine; 3-hydroxy-L-proline; 3'-methyl-L-histidine; 3-methyl-L-lanthionine; 3'-phospho-L-histidine; 4'-(L-tryptophan)-L-tryptophyl quinone; 42 N-cysteinyl-glycosylphosphatidylinositolethanolamine; 43 -(T-L-histidyl)-L-tyrosine; 4-hydroxy-L-arginine; 4-hydroxy-L-lysine; 4-hydroxy-L-proline; 5'-(N6-L-lysine)-L-topaquinone; 5-hydroxy-L-lysine; 5-methyl-L-arginine; alpha-l-microglobulin-Ig alpha complex chromophore; bis-L-cysteinyl bis-L-histidino diiron disulfide; bis-L--cysteinyl-L-N3'-histidino-L-serinyI tetrairon' tetrasulfide; chondroitin sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; D-alanine; D-allo-isoleucine; D-asparagine; dehydroalanine; dehydrotyrosine; dermatan 4-sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; D-glucuronyl-N-glycine; dipyrrolylmethanemethyl-L-cysteine; D-leucine; D-methionine; D-phenylalanine; D-serine; D-tryptophan; glycine amide; glycine oxazolecarboxylic acid; glycine thiazolecarboxylic acid; heme P450-bis-L-cysteine-L-tyrosine; heme-bis-L-cysteine; hemediol-L-aspartyl ester-L-glutamyl ester; hemediol-L-aspartyl ester-L-glutamyl ester-L-methionine sulfonium; heme-L-cysteine; heme-L-histidine; heparan sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; heme P450-bis-L-cysteine-L-lysine; hexakis-L-cysteinyl hexairon hexasulfide; keratan sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-threonine; L oxoalanine- lactic acid; L phenyllactic acid; l'-(8alpha-FAD)-L-histidine; L-2'.4',5'-topaquinone; L-3',4'-dihydroxyphenylalanine; L-3'.4'.5'-trihydroxyphenylalanine; L-4'-bromophenylalanine; L-6'-bromotryptophan; L-alanine amide; L-alanyl imidazolinone glycine; L-allysine; L-arginine amide; L-asparagine amide; L-aspartic 4-phosphoric anhydride; L-aspartic acid 1-amide; L-beta-methylthioaspartic acid; L-bromohistidine; L-citrulline; L-cysteine amide; L-cysteine glutathione disulfide; L-cysteine methyl disulfide;

L-cysteine methyl ester; L-cysteine oxazolecarboxylic acid; L-cysteine oxazolinecarboxylic acid; L-cysteine persulfide; L-cysteine sulfenic acid; L-cysteine sulfinic acid; L-cysteine thiazolecarboxylic acid; L-cysteinyl homocitryl molybdenum-heptairon-nonasulfide; L-cysteinyl imidazolinone glycine; L-cysteinyl molybdopterin; L-cysteinyl molybdopterin guanine dinucleotide; L-cystine; L-erythro-beta-hydroxyasparagine; L-erythro-beta-hydroxyaspartic acid; L-gamma-carboxyglutamic acid; L-glutamic acid 1-amide; L-glutamic acid 5-methyl ester; L-glutamine amide; L-glutamyl 5-glycerylphosphorylethanolamine; L-histidine amide; L-isoglutamyl-polyglutamic acid; L-isoglutamyl-polyglycine; L-isoleucine amide; L-lanthionine; L-leucine amide; L-lysine amide; L-lysine thiazolecarboxylic acid; L-lysinoalanine; L-methionine amide; L-methionine sulfone; L-phenyalanine thiazolecarboxylic acid; L-phenylalanine amide; L-proline amide; L-selenocysteine; L-selenocysteinyl molybdopterin guanine dinucleotide; L-serine amide; L-serine thiazolecarboxylic acid; L-seryl imidazolinone glycine; L-T-bromophenylalanine; L-T-bromophenylalanine; L-threonine amide; L-thyroxine; L-tryptophan amide; L-tryptophyl quinone; L-tyrosine amide; L-valine amide; meso-lanthionine; N-(L-glutamyl)-L-tyrosine; N-(L-isoaspartyl)-glycine; N-(L-isoaspartyl)-L-cysteine; N,N,N-trimethyl-L-alanine; N,N-dimethyl-L-proline; N2-acetyl-L-lysine; N2-succinyl-L-tryptophan; N4-(ADP-ribosyl)-L-asparagine; N4-glycosyl-L-asparagine; N4-hydroxymethyl-L-asparagine; N4-methyl-L-asparagine; N5-methyl-L-glutamine; N6- 1 -carboxyethyl-L-lysine; N6-(4-amino hydroxybutyl)-L-lysine; N6-(L-isoglutamyl)-L-lysine; N6-(phospho-5'-adenosine)-L-lysine; N6-(phospho-5'-guanosine)-L-tysine; N6,N6,N6-trimethyl-L-lysine; N6,N6-dimethyl-L-lysine; N6-acetyl-L-lysine; N6-biotinyl-L-lysine; N6-carboxy-L-lysine; N6-formyl-L-lysine; N6-glycyl-L-lysine; N6-lipoyl-L-lysine; N6-methyl-L-lysine; N6-methyl-N6-poly(N-methyl-propylamine)-L-lysine; N6-mureinyl-L-lysine; N6-myristoyl-L-lysine; N6-palmitoyl-L-lysine; N6-pyridoxal phosphate-L-lysine; N6-pyruvic acid 2-iminyl-L-lysine; N6-retinal-L-lysine; N-acetylglycine; N-acetyl-L-glutamine; N-acetyl-L-alanine; N-acetyl-L-aspartic acid; N-acetyl-L-cysteine; N-acetyl-L-glutamic acid; N-acetyl-L-isoleucine; N-acetyl-L-methionine; N-acetyl-L-proline; N-acetyl-L-serine; N-acetyl-L-threonine; N-acetyl-L-tyrosine; N-acetyl-L-valine; N-alanyl-glycosylphosphatidylinositolethanolamine; N-asparaginyl-glycosylphosphatidylinositolethanolamine; N-aspartyl-glycosylphosphatidylinositolethanolamine; N-formylglycine; N-formyl-L-methionine; N-glycyl-glycosylphosphatidylinositolethanolamine; N-L-glutamyl-poly-L-glutamic acid; N-

methylglycine; N-methyl-L-alanine; N-methyl-L-methionine; N-methyl-L-phenylalanine; N-myristoyl-glycine; N-palmitoyl-L-cysteine; N-pyruvic acid 2-iminyl-L-cysteine; N-pyruvic acid 2-iminyl-L-valine; N-seryl-glycosylphosphatidylinositolethanolamine; N-seryl-glycosyOSPhingolipidinositolethanolamine; O-(ADP-ribosyl)-L-serine; O-(phospho-5'-adenosine)-L-threonine; O-(phospho-5'-DNA)-L-serine; O-(phospho-5'-DNA)-L-threonine; O-(phospho-5'rRNA)-L-serine; O-(phosphoribosyl dephospho-coenzyme A)-L-serine; O-(sn-l-glycerophosphoryl)-L-serine; O4'-(8alpha-FAD)-L-tyrosine; O4'-(phospho-5'-adenosine)-L-tyrosine; O4'-(phospho-5'-DNA)-L-tyrosine; O4'-(phospho-5'-RNA)-L-tyrosine; O4'-(phospho-5'-uridine)-L-tyrosine; O4-glycosyl-L-hydroxyproline; O4'-glycosyl-L-tyrosine; O4'-sulfo-L-tyrosine; O5-glycosyl-L-hydroxylysine; O-glycosyl-L-serine; O-glycosyl-L-threonine; omega-N-(ADP-ribosyl)-L-arginine; omega-N-omega-N'-dimethyl-L-arginine; omega-N-methyl-L-arginine; omega-N-omega-N-dimethyl-L-arginine; omega-N-phospho-L-arginine; O'octanoyl-L-serine; O-palmitoyl-L-serine; O-palmitoyl-L-threonine; O-phospho-L-serine; O-phospho-L-threonine; O-phosphopantetheine-L-serine; phycoerythrobilin-bis-L-cysteine; phycourobilin-bis-L-cysteine; pyrroloquinoline quinone; pyruvic acid; S hydroxycinnamyl-L-cysteine; S-(2-aminovinyl) methyl-D-eysteine; S-(2-aminovinyl)-D-cysteine; S-(6-FW-L-cysteine; S-(8alpha-FAD)-L-cysteine; S-(ADP-ribosyl)-L-cysteine; S-(L-isoglutamyl)-L-cysteine; S-12-hydroxyfarnesyl-L-cysteine; S-acetyl-L-cysteine; S-diacylglycerol-L-cysteine; S-diphytanylglycerot diether-L-cysteine; S-farnesyl-L-cysteine; S-geranylgeranyl-L-cysteine; S-glycosyl-L-cysteine; S-glycyl-L-cysteine; S-methyl-L-cysteine; S-nitrosyl-L-cysteine; S-palmitoyl-L-cysteine; S-phospho-L-cysteine; S-phycobiliviolin-L-cysteine; S-phycocyanobilin-L-cysteine; S-phycoerythrobilin-L-cysteine; S-phytochromobilin-L-cysteine; S-selenyl-L-cysteine; S-sulfo-L-cysteine; tetrakis-L-cysteinyl diiron disulfide; tetrakis-L-cysteinyl iron; tetrakis-L-cysteinyl tetrairon tetrasulfide; trans-2,3-cis 4-dihydroxy-L-proline; tris-L-cysteinyl triiron tetrasulfide; tris-L-cysteinyl triiron trisulfide; tris-L-cysteinyl-L-aspartato tetrairon tetrasulfide; tris-L-cysteinyl-L-cysteine persulfido-bis-L-glutamato-L-histidino tetrairon disulfide trioxide; tris-L-cysteinyl-L-N3'-histidino tetrairon tetrasulfide; tris-L-cysteinyl-L-Nl'-histidino tetrairon tetrasulfide; and tris-L-cysteinyl-L-serinyl tetrairon tetrasulfide.

Additional examples of PTMs may be found in web sites such as the Delta Mass database based on Krishna, R. G. and F. Wold (1998). Posttranslational Modifications. Proteins - Analysis and Design. R. H. Angeletti. San Diego, Academic Press. 1: 121-206. ;

Methods in Enzymology, 193, J.A. McClosky (ed) (1990), pages 647-660; Methods in Protein Sequence Analysis edited by Kazutomo Imahori and Fumio Sakiyama, Plenum Press, (1993) "Post-translational modifications of proteins" R.G. Krishna and F. Wold pages 167-172; "GlycoSuiteDB: a new curated relational database of glycoprotein glycan structures and their biological sources" Cooper et al. Nucleic Acids Res. 29; 332-335 (2001) "O-GLYCBASE version 4.0: a revised database of O-glycosylated proteins" Gupta et al. Nucleic Acids Research, 27: 370-372 (1999); and "PhosphoBase, a database of phosphorylation sites: release 2.0.", Kreegipuu et al.Nucleic Acids Res 27(1):237-239 (1999) see also,WO 02/21139A2, the disclosure of which is incorporated herein by reference in its entirety.

Tumorigenesis is often accompanied by alterations in the post-translational modifications of proteins. Thus, in another embodiment, the invention provides polypeptides from cancerous cells or tissues that have altered post-translational modifications compared to the post-translational modifications of polypeptides from normal cells or tissues. A number of altered post-translational modifications are known. One common alteration is a change in phosphorylation state, wherein the polypeptide from the cancerous cell or tissue is hyperphosphorylated or hypophosphorylated compared to the polypeptide from a normal tissue, or wherein the polypeptide is phosphorylated on different residues than the polypeptide from a normal cell. Another common alteration is a change in glycosylation state, wherein the polypeptide from the cancerous cell or tissue has more or less glycosylation than the polypeptide from a normal tissue, and/or wherein the polypeptide from the cancerous cell or tissue has a different type of glycosylation than the polypeptide from a noncancerous cell or tissue. Changes in glycosylation may be critical because carbohydrate-protein and carbohydrate-carbohydrate interactions are important in cancer cell progression, dissemination and invasion. See, e.g., Barchi, *Curr. Pharm. Des.* 6: 485-501 (2000), Verma, *Cancer Biochem. Biophys.* 14: 151-162 (1994) and Dennis et al., *Bioessays* 5: 412-421 (1999).

Another post-translational modification that may be altered in cancer cells is prenylation. Prenylation is the covalent attachment of a hydrophobic prenyl group (either farnesyl or geranylgeranyl) to a polypeptide. Prenylation is required for localizing a protein to a cell membrane and is often required for polypeptide function. For instance, the Ras superfamily of GTPase signalling proteins must be prenylated for function in a

cell. See, e.g., Prendergast et al., *Semin. Cancer Biol.* 10: 443-452 (2000) and Khwaja et al., *Lancet* 355: 741-744 (2000).

Other post-translation modifications that may be altered in cancer cells include, without limitation, polypeptide methylation, acetylation, arginylation or racemization of amino acid residues. In these cases, the polypeptide from the cancerous cell may exhibit either increased or decreased amounts of the post-translational modification compared to the corresponding polypeptides from noncancerous cells.

Other polypeptide alterations in cancer cells include abnormal polypeptide cleavage of proteins and aberrant protein-protein interactions. Abnormal polypeptide cleavage may be cleavage of a polypeptide in a cancerous cell that does not usually occur in a normal cell, or a lack of cleavage in a cancerous cell, wherein the polypeptide is cleaved in a normal cell. Aberrant protein-protein interactions may be either covalent cross-linking or non-covalent binding between proteins that do not normally bind to each other. Alternatively, in a cancerous cell, a protein may fail to bind to another protein to which it is bound in a noncancerous cell. Alterations in cleavage or in protein-protein interactions may be due to over- or underproduction of a polypeptide in a cancerous cell compared to that in a normal cell, or may be due to alterations in post-translational modifications (see above) of one or more proteins in the cancerous cell. See, e.g., Henschen-Edman, *Ann. N.Y. Acad. Sci.* 936: 580-593 (2001).

Alterations in polypeptide post-translational modifications, as well as changes in polypeptide cleavage and protein-protein interactions, may be determined by any method known in the art. For instance, alterations in phosphorylation may be determined by using anti-phosphoserine, anti-phosphothreonine or anti-phosphotyrosine antibodies or by amino acid analysis. Glycosylation alterations may be determined using antibodies specific for different sugar residues, by carbohydrate sequencing, or by alterations in the size of the glycoprotein, which can be determined by, e.g., SDS polyacrylamide gel electrophoresis (PAGE). Other alterations of post-translational modifications, such as prenylation, racemization, methylation, acetylation and arginylation, may be determined by chemical analysis, protein sequencing, amino acid analysis, or by using antibodies specific for the particular post-translational modifications. Changes in protein-protein interactions and in polypeptide cleavage may be analyzed by any method known in the art including, without limitation, non-denaturing PAGE (for non-covalent protein-protein interactions), SDS

PAGE (for covalent protein-protein interactions and protein cleavage), chemical cleavage, protein sequencing or immunoassays.

In another embodiment, the invention provides polypeptides that have been post-translationally modified. In one embodiment, polypeptides may be modified enzymatically or chemically, by addition or removal of a post-translational modification. For example, a polypeptide may be glycosylated or deglycosylated enzymatically. Similarly, polypeptides may be phosphorylated using a purified kinase, such as a MAP kinase (e.g, p38, ERK, or JNK) or a tyrosine kinase (e.g., Src or erbB2). A polypeptide may also be modified through synthetic chemistry. Alternatively, one may isolate the polypeptide of interest from a cell or tissue that expresses the polypeptide with the desired post-translational modification. In another embodiment, a nucleic acid molecule encoding the polypeptide of interest is introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide in the desired fashion. If the polypeptide does not contain a motif for a desired post-translational modification, one may alter the post-translational modification by mutating the nucleic acid sequence of a nucleic acid molecule encoding the polypeptide so that it contains a site for the desired post-translational modification. Amino acid sequences that may be post-translationally modified are known in the art. See, e.g., the programs described above on the website www.expasy.org. The nucleic acid molecule may also be introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide. Similarly, one may delete sites that are post-translationally modified by either mutating the nucleic acid sequence so that the encoded polypeptide does not contain the post-translational modification motif, or by introducing the native nucleic acid molecule into a host cell that is not capable of post-translationally modifying the encoded polypeptide.

It will be appreciated, as is well known and as noted above, that polypeptides are not always entirely linear. For instance, polypeptides may be branched as a result of ubiquitination, and they may be circular, with or without branching, generally as a result of posttranslation events, including natural processing event and events brought about by human manipulation which do not occur naturally. Circular, branched and branched circular polypeptides may be synthesized by non-translation natural process and by entirely synthetic methods, as well. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. In fact, blockage of the amino or carboxyl group in a polypeptide, or both, by a

covalent modification, is common in naturally occurring and synthetic polypeptides and such modifications may be present in polypeptides of the present invention, as well. For instance, the amino terminal residue of polypeptides made in *E. coli*, prior to proteolytic processing, almost invariably will be N-formylmethionine.

Useful post-synthetic (and post-translational) modifications include conjugation to detectable labels, such as fluorophores. A wide variety of amine-reactive and thiol-reactive fluorophore derivatives have been synthesized that react under nondenaturing conditions with N-terminal amino groups and epsilon amino groups of lysine residues, on the one hand, and with free thiol groups of cysteine residues, on the other.

Kits are available commercially that permit conjugation of proteins to a variety of amine-reactive or thiol-reactive fluorophores: Molecular Probes, Inc. (Eugene, OR, USA), *e.g.*, offers kits for conjugating proteins to Alexa Fluor 350, Alexa Fluor 430, Fluorescein-EX, Alexa Fluor 488, Oregon Green 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, and Texas Red-X.

A wide variety of other amine-reactive and thiol-reactive fluorophores are available commercially (Molecular Probes, Inc., Eugene, OR, USA), including Alexa Fluor® 350, Alexa Fluor® 488, Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from Molecular Probes, Inc., Eugene, OR, USA).

The polypeptides of the present invention can also be conjugated to fluorophores, other proteins, and other macromolecules, using bifunctional linking reagents. Common homobifunctional reagents include, *e.g.*, APG, AEDP, BASED, BMB, BMDB, BMH, BMOE, BM[PEO]3, BM[PEO]4, BS3, BSOCOES, DFDNB, DMA, DMP, DMS, DPDPB, DSG, DSP (Lomant's Reagent), DSS, DST, DTBP, DTME, DTSSP, EGS, HBVS, Sulfo-BSOCOES, Sulfo-DST, Sulfo-EGS (all available from Pierce, Rockford, IL, USA); common heterobifunctional cross-linkers include ABH, AMAS, ANB-NOS, APDP, ASBA, BMPA, BMPH, BMPS, EDC, EMCA, EMCH, EMCS, KMUA, KMUH, GMBS,

LC-SMCC, LC-SPDP, MBS, M2C2H, MPBH, MSA, NHS-ASA, PDPH, PMPI, SADP, SAED, SAND, SANPAH, SASD, SATP, SBAP, SFAD, SIA, SIAB, SMCC, SMPB, SMPH, SMPT, SPDP, Sulfo-EMCS, Sulfo-GMBS, Sulfo-HSAB, Sulfo-KMUS, Sulfo-LC-SPDP, Sulfo-MBS, Sulfo-NHS-LC-ASA, Sulfo-SADP, Sulfo-SANPAH, Sulfo-SIAB, Sulfo-SMCC, Sulfo-SMPB, Sulfo-LC-SMPT, SVSB, TFCS (all available Pierce, Rockford, IL, USA).

Polypeptides of the present invention, including full length polypeptides, fragments and fusion proteins, can be conjugated, using such cross-linking reagents, to fluorophores that are not amine- or thiol-reactive. Other labels that usefully can be conjugated to polypeptides of the present invention include radioactive labels, echosonographic contrast reagents, and MRI contrast agents.

Polypeptides of the present invention, including full length polypeptide, fragments and fusion proteins, can also usefully be conjugated using cross-linking agents to carrier proteins, such as KLH, bovine thyroglobulin, and even bovine serum albumin (BSA), to increase immunogenicity for raising anti-OSP antibodies.

Polypeptides of the present invention, including full length polypeptide, fragments and fusion proteins, can also usefully be conjugated to polyethylene glycol (PEG); PEGylation increases the serum half life of proteins administered intravenously for replacement therapy. Delgado *et al.*, *Crit. Rev. Ther. Drug Carrier Syst.* 9(3-4): 249-304 (1992); Scott *et al.*, *Curr. Pharm. Des.* 4(6): 423-38 (1998); DeSantis *et al.*, *Curr. Opin. Biotechnol.* 10(4): 324-30 (1999). PEG monomers can be attached to the protein directly or through a linker, with PEGylation using PEG monomers activated with tresyl chloride (2,2,2-trifluoroethanesulphonyl chloride) permitting direct attachment under mild conditions.

Polypeptides of the present invention are also inclusive of analogs of a polypeptide encoded by a nucleic acid molecule according to the instant invention. In a preferred embodiment, this polypeptide is a OSP. In a more preferred embodiment, this polypeptide is derived from a polypeptide having part or all of the amino acid sequence of SEQ ID NO: 249-396. Also preferred is an analog polypeptide comprising one or more substitutions of non-natural amino acids or non-native inter-residue bonds compared to the naturally occurring polypeptide. In one embodiment, the analog is structurally similar to a OSP, but one or more peptide linkages is replaced by a linkage selected from the group consisting of --CH_2NH--, --CH_2S--, --CH_2-CH_2--, --CH=CH--(cis and trans), --$COCH_2$--,

--CH(OH)CH_2-- and –CH_2SO--. In another embodiment, the analog comprises substitution of one or more amino acids of a OSP with a D-amino acid of the same type or other non-natural amino acid in order to generate more stable peptides. D-amino acids can readily be incorporated during chemical peptide synthesis: peptides assembled from D-amino acids are more resistant to proteolytic attack; incorporation of D-amino acids can also be used to confer specific three-dimensional conformations on the peptide. Other amino acid analogues commonly added during chemical synthesis include ornithine, norleucine, phosphorylated amino acids (typically phosphoserine, phosphothreonine, phosphotyrosine), L-malonyltyrosine, a non-hydrolyzable analog of phosphotyrosine (*see, e.g.,* Kole *et al.*, *Biochem. Biophys. Res. Com.* 209: 817-821 (1995)), and various halogenated phenylalanine derivatives.

Non-natural amino acids can be incorporated during solid phase chemical synthesis or by recombinant techniques, although the former is typically more common. Solid phase chemical synthesis of peptides is well established in the art. Procedures are described, *inter alia*, in Chan *et al.* (eds.), Fmoc Solid Phase Peptide Synthesis: A Practical Approach (Practical Approach Series), Oxford Univ. Press (March 2000); Jones, Amino Acid and Peptide Synthesis (Oxford Chemistry Primers, No 7), Oxford Univ. Press (1992); and Bodanszky, Principles of Peptide Synthesis (Springer Laboratory), Springer Verlag (1993).

Amino acid analogues having detectable labels are also usefully incorporated during synthesis to provide derivatives and analogs. Biotin, for example can be added using biotinoyl--(9-fluorenylmethoxycarbonyl)-L-lysine (FMOC biocytin) (Molecular Probes, Eugene, OR, USA). Biotin can also be added enzymatically by incorporation into a fusion protein of a *E. coli* BirA substrate peptide. The FMOC and *t*BOC derivatives of dabcyl-L-lysine (Molecular Probes, Inc., Eugene, OR, USA) can be used to incorporate the dabcyl chromophore at selected sites in the peptide sequence during synthesis. The aminonaphthalene derivative EDANS, the most common fluorophore for pairing with the dabcyl quencher in fluorescence resonance energy transfer (FRET) systems, can be introduced during automated synthesis of peptides by using EDANS--FMOC–L-glutamic acid or the corresponding *t*BOC derivative (both from Molecular Probes, Inc., Eugene, OR, USA). Tetramethylrhodamine fluorophores can be incorporated during automated FMOC synthesis of peptides using (FMOC)--TMR-L-lysine (Molecular Probes, Inc. Eugene, OR, USA).

Other useful amino acid analogues that can be incorporated during chemical synthesis include aspartic acid, glutamic acid, lysine, and tyrosine analogues having allyl side-chain protection (Applied Biosystems, Inc., Foster City, CA, USA); the allyl side chain permits synthesis of cyclic, branched-chain, sulfonated, glycosylated, and phosphorylated peptides.

A large number of other FMOC-protected non-natural amino acid analogues capable of incorporation during chemical synthesis are available commercially, including, *e.g.*, Fmoc-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid, Fmoc-3-endo-aminobicyclo[2.2.1]heptane-2-endo-carboxylic acid, Fmoc-3-exo-aminobicyclo[2.2.1]heptane-2-exo-carboxylic acid, Fmoc-3-endo-amino-bicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid, Fmoc-3-exo-amino-bicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid, Fmoc-cis-2-amino-1-cyclohexanecarboxylic acid, Fmoc-trans-2-amino-1-cyclohexanecarboxylic acid, Fmoc-1-amino-1-cyclopentanecarboxylic acid, Fmoc-cis-2-amino-1-cyclopentanecarboxylic acid, Fmoc-1-amino-1-cyclopropanecarboxylic acid, Fmoc-D-2-amino-4-(ethylthio)butyric acid, Fmoc-L-2-amino-4-(ethylthio)butyric acid, Fmoc-L-buthionine, Fmoc-S-methyl-L-Cysteine, Fmoc-2-aminobenzoic acid (anthranillic acid), Fmoc-3-aminobenzoic acid, Fmoc-4-aminobenzoic acid, Fmoc-2-aminobenzophenone-2'-carboxylic acid, Fmoc-N-(4-aminobenzoyl)-β-alanine, Fmoc-2-amino-4,5-dimethoxybenzoic acid, Fmoc-4-aminohippuric acid, Fmoc-2-amino-3-hydroxybenzoic acid, Fmoc-2-amino-5-hydroxybenzoic acid, Fmoc-3-amino-4-hydroxybenzoic acid, Fmoc-4-amino-3-hydroxybenzoic acid, Fmoc-4-amino-2-hydroxybenzoic acid, Fmoc-5-amino-2-hydroxybenzoic acid, Fmoc-2-amino-3-methoxybenzoic acid, Fmoc-4-amino-3-methoxybenzoic acid, Fmoc-2-amino-3-methylbenzoic acid, Fmoc-2-amino-5-methylbenzoic acid, Fmoc-2-amino-6-methylbenzoic acid, Fmoc-3-amino-2-methylbenzoic acid, Fmoc-3-amino-4-methylbenzoic acid, Fmoc-4-amino-3-methylbenzoic acid, Fmoc-3-amino-2-naphtoic acid, Fmoc-D,L-3-amino-3-phenylpropionic acid, Fmoc-L-Methyldopa, Fmoc-2-amino-4,6-dimethyl-3-pyridinecarboxylic acid, Fmoc-D,L-amino-2-thiophenacetic acid, Fmoc-4-(carboxymethyl)piperazine, Fmoc-4-carboxypiperazine, Fmoc-4-(carboxymethyl)homopiperazine, Fmoc-4-phenyl-4-piperidinecarboxylic acid, Fmoc-L-1,2,3,4-tetrahydronorharman-3-carboxylic acid, Fmoc-L-thiazolidine-4-carboxylic acid, all available from The Peptide Laboratory (Richmond, CA, USA).

Non-natural residues can also be added biosynthetically by engineering a suppressor tRNA, typically one that recognizes the UAG stop codon, by chemical aminoacylation with the desired unnatural amino acid. Conventional site-directed mutagenesis is used to introduce the chosen stop codon UAG at the site of interest in the protein gene. When the acylated suppressor tRNA and the mutant gene are combined in an *in vitro* transcription/translation system, the unnatural amino acid is incorporated in response to the UAG codon to give a protein containing that amino acid at the specified position. Liu *et al.*, *Proc. Natl Acad. Sci. USA* 96(9): 4780-5 (1999); Wang *et al.*, *Science* 292(5516): 498-500 (2001).

Fusion Proteins

Another aspect of the present invention relates to the fusion of a polypeptide of the present invention to heterologous polypeptides. In a preferred embodiment, the polypeptide of the present invention is a OSP. In a more preferred embodiment, the polypeptide of the present invention that is fused to a heterologous polypeptide comprises part or all of the amino acid sequence of SEQ ID NO: 249-396, or is a mutein, homologous polypeptide, analog or derivative thereof. In an even more preferred embodiment, the fusion protein is encoded by a nucleic acid molecule comprising all or part of the nucleic acid sequence of SEQ ID NO: 1-248, or comprises all or part of a nucleic acid sequence that selectively hybridizes or is homologous to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248.

The fusion proteins of the present invention will include at least one fragment of a polypeptide of the present invention, which fragment is at least 6, typically at least 8, often at least 15, and usefully at least 16, 17, 18, 19, or 20 amino acids long. The fragment of the polypeptide of the present to be included in the fusion can usefully be at least 25 amino acids long, at least 50 amino acids long, and can be at least 75, 100, or even 150 amino acids long. Fusions that include the entirety of a polypeptide of the present invention have particular utility.

The heterologous polypeptide included within the fusion protein of the present invention is at least 6 amino acids in length, often at least 8 amino acids in length, and preferably at least 15, 20, or 25 amino acids in length. Fusions that include larger polypeptides, such as the IgG Fc region, and even entire proteins (such as GFP chromophore-containing proteins) are particularly useful.

As described above in the description of vectors and expression vectors of the present invention, which discussion is incorporated here by reference in its entirety, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those designed to facilitate purification and/or visualization of recombinantly-expressed proteins. *See, e.g.*, Ausubel, Chapter 16, (1992), *supra*. Although purification tags can also be incorporated into fusions that are chemically synthesized, chemical synthesis typically provides sufficient purity that further purification by HPLC suffices; however, visualization tags as above described retain their utility even when the protein is produced by chemical synthesis, and when so included render the fusion proteins of the present invention useful as directly detectable markers of the presence of a polypeptide of the invention.

As also discussed above, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those that facilitate secretion of recombinantly expressed proteins into the periplasmic space or extracellular milieu for prokaryotic hosts or into the culture medium for eukaryotic cells through incorporation of secretion signals and/or leader sequences. For example, a His^6 tagged protein can be purified on a Ni affinity column and a GST fusion protein can be purified on a glutathione affinity column. Similarly, a fusion protein comprising the Fc domain of IgG can be purified on a Protein A or Protein G column and a fusion protein comprising an epitope tag such as myc can be purified using an immunoaffinity column containing an anti-c-myc antibody. It is preferable that the epitope tag be separated from the protein encoded by the essential gene by an enzymatic cleavage site that can be cleaved after purification. See also the discussion of nucleic acid molecules encoding fusion proteins that may be expressed on the surface of a cell.

Other useful fusion proteins of the present invention include those that permit use of the polypeptide of the present invention as bait in a yeast two-hybrid system. *See* Bartel *et al.* (eds.), The Yeast Two-Hybrid System, Oxford University Press (1997); Zhu *et al.*, Yeast Hybrid Technologies, Eaton Publishing (2000); Fields *et al.*, *Trends Genet.* 10(8): 286-92 (1994); Mendelsohn *et al.*, *Curr. Opin. Biotechnol.* 5(5): 482-6 (1994); Luban *et al.*, *Curr. Opin. Biotechnol.* 6(1): 59-64 (1995); Allen *et al.*, *Trends Biochem. Sci.* 20(12): 511-6 (1995); Drees, *Curr. Opin. Chem. Biol.* 3(1): 64-70 (1999); Topcu *et al.*, *Pharm. Res.* 17(9): 1049-55 (2000); Fashena *et al.*, *Gene* 250(1-2): 1-14 (2000); Colas *et al.*, *Nature* 380, 548-550 (1996); Norman, T. *et al.*, *Science* 285, 591-595 (1999);

Fabbrizio *et al.*, *Oncogene* 18, 4357-4363 (1999); Xu *et al.*, *Proc Natl Acad Sci U S A.* 94, 12473-12478 (1997); Yang, *et al.*, *Nuc. Acids Res.* 23, 1152-1156 (1995); Kolonin *et al.*, *Proc Natl Acad Sci U S A* 95, 14266-14271 (1998); Cohen *et al.*, *Proc Natl Acad Sci U S A* 95, 14272-14277 (1998); Uetz, *et al. Nature* 403, 623-627(2000); Ito, *et al.*, *Proc Natl Acad Sci U S A* 98, 4569-4574 (2001). Typically, such fusion is to either *E. coli* LexA or yeast GAL4 DNA binding domains. Related bait plasmids are available that express the bait fused to a nuclear localization signal.

Other useful fusion proteins include those that permit display of the encoded polypeptide on the surface of a phage or cell, fusions to intrinsically fluorescent proteins, such as green fluorescent protein (GFP), and fusions to the IgG Fc region, as described above.

The polypeptides of the present invention can also usefully be fused to protein toxins, such as Pseudomonas exotoxin A, diphtheria toxin, shiga toxin A, anthrax toxin lethal factor, ricin, in order to effect ablation of cells that bind or take up the proteins of the present invention.

Fusion partners include, *inter alia*, *myc*, hemagglutinin (HA), GST, immunoglobulins, β-galactosidase, biotin trpE, protein A, β-lactamase, α-amylase, maltose binding protein, alcohol dehydrogenase, polyhistidine (for example, six histidine at the amino and/or carboxyl terminus of the polypeptide), lacZ, green fluorescent protein (GFP), yeast α mating factor, GAL4 transcription activation or DNA binding domain, luciferase, and serum proteins such as ovalbumin, albumin and the constant domain of IgG. *See, e.g.*, Ausubel (1992), *supra* and Ausubel (1999), *supra*. Fusion proteins may also contain sites for specific enzymatic cleavage, such as a site that is recognized by enzymes such as Factor XIII, trypsin, pepsin, or any other enzyme known in the art. Fusion proteins will typically be made by either recombinant nucleic acid methods, as described above, chemically synthesized using techniques well known in the art (*e.g.*, a Merrifield synthesis), or produced by chemical cross-linking.

Another advantage of fusion proteins is that the epitope tag can be used to bind the fusion protein to a plate or column through an affinity linkage for screening binding proteins or other molecules that bind to the OSP.

As further described below, the polypeptides of the present invention can readily be used as specific immunogens to raise antibodies that specifically recognize polypeptides of the present invention including OSPs and their allelic variants and

homologues. The antibodies, in turn, can be used, *inter alia*, specifically to assay for the polypeptides of the present invention, particularly OSPs, *e.g.* by ELISA for detection of protein fluid samples, such as serum, by immunohistochemistry or laser scanning cytometry, for detection of protein in tissue samples, or by flow cytometry, for detection of intracellular protein in cell suspensions, for specific antibody-mediated isolation and/or purification of OSPs, as for example by immunoprecipitation, and for use as specific agonists or antagonists of OSPs.

One may determine whether polypeptides of the present invention including OSPs, muteins, homologous proteins or allelic variants or fusion proteins of the present invention are functional by methods known in the art. For instance, residues that are tolerant of change while retaining function can be identified by altering the polypeptide at known residues using methods known in the art, such as alanine scanning mutagenesis, Cunningham *et al.*, *Science* 244(4908): 1081-5 (1989); transposon linker scanning mutagenesis, Chen *et al.*, *Gene* 263(1-2): 39-48 (2001); combinations of homolog- and alanine-scanning mutagenesis, Jin *et al.*, *J. Mol. Biol.* 226(3): 851-65 (1992); combinatorial alanine scanning, Weiss *et al.*, *Proc. Natl. Acad. Sci USA* 97(16): 8950-4 (2000), followed by functional assay. Transposon linker scanning kits are available commercially (New England Biolabs, Beverly, MA, USA, catalog. no. E7-102S; EZ::TN™ In-Frame Linker Insertion Kit, catalogue no. EZI04KN, (Epicentre Technologies Corporation, Madison, WI, USA).

Purification of the polypeptides or fusion proteins of the present invention is well known and within the skill of one having ordinary skill in the art. *See, e.g.,* Scopes, Protein Purification, 2d ed. (1987). Purification of recombinantly expressed polypeptides is described above. Purification of chemically-synthesized peptides can readily be effected, *e.g.*, by HPLC.

Accordingly, it is an aspect of the present invention to provide the isolated polypeptides or fusion proteins of the present invention in pure or substantially pure form in the presence of absence of a stabilizing agent. Stabilizing agents include both proteinaceous and non-proteinaceous material and are well known in the art. Stabilizing agents, such as albumin and polyethylene glycol (PEG) are known and are commercially available.

Although high levels of purity are preferred when the isolated polypeptide or fusion protein of the present invention are used as therapeutic agents, such as in vaccines

and replacement therapy, the isolated polypeptides of the present invention are also useful at lower purity. For example, partially purified polypeptides of the present invention can be used as immunogens to raise antibodies in laboratory animals.

In a preferred embodiment, the purified and substantially purified polypeptides of the present invention are in compositions that lack detectable ampholytes, acrylamide monomers, bis-acrylamide monomers, and polyacrylamide.

The polypeptides or fusion proteins of the present invention can usefully be attached to a substrate. The substrate can be porous or solid, planar or non-planar; the bond can be covalent or noncovalent. For example, the peptides of the invention may be stabilized by covalent linkage to albumin. See, U.S. Patent No. 5,876,969, the contents of which are hereby incorporated in its entirety.

For example, the polypeptides or fusion proteins of the present invention can usefully be bound to a porous substrate, commonly a membrane, typically comprising nitrocellulose, polyvinylidene fluoride (PVDF), or cationically derivatized, hydrophilic PVDF; so bound, the polypeptides or fusion proteins of the present invention can be used to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized polypeptide or fusion protein of the present invention.

As another example, the polypeptides or fusion proteins of the present invention can usefully be bound to a substantially nonporous substrate, such as plastic, to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized protein of the present invention. Such plastics include polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene, polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof; when the assay is performed in a standard microtiter dish, the plastic is typically polystyrene.

The polypeptides and fusion proteins of the present invention can also be attached to a substrate suitable for use as a surface enhanced laser desorption ionization source; so attached, the polypeptide or fusion protein of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound polypeptide or fusion protein to indicate biologic interaction there between. The polypeptides or fusion proteins of the present invention can also be attached to a substrate suitable for use in surface plasmon resonance detection; so attached, the polypeptide or fusion protein of the present invention is useful for binding and then

detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound polypeptide or fusion protein to indicate biological interaction there between.

Alternative Transcripts

In antother aspect, the present invention provides splice variants of genes and proteins encoded thereby. The identification of a novel splice varaint which encodes an amino acid sequence with a novel region can be targeted for the generation of reagents for use in detection and/or treatment of cancer. The novel amino acid sequence may lead to a unique protein structure, protein subcellular localization, biochemical processing or function of the splice varaint. This information can be used to directly or indirectly facilitate the generation of additional or novel therapeutics or diagnostics. The nucleotide sequence in this novel splice variant can be used as a nucleic acid probe for the diagnosis and/or treatment of cancer.

Specifically, the newly identified sequences may enable the production of new antibodies or compounds directed against the novel region for use as a therapeutic or diagnostic. Alternatively, the newly identified sequences may alter the biochemical or biological properties of the encoded protein in such a way as to enable the generation of improved or different therapeutics targeting this protein.

Antibodies

In another aspect, the invention provides antibodies, including fragments and derivatives thereof, that bind specifically to polypeptides encoded by the nucleic acid molecules of the invention. In a preferred embodiment, the antibodies are specific for a polypeptide that is a OSP, or a fragment, mutein, derivative, analog or fusion protein thereof. In a more preferred embodiment, the antibodies are specific for a polypeptide that comprises SEQ ID NO: 249-396, or a fragment, mutein, derivative, analog or fusion protein thereof.

The antibodies of the present invention can be specific for linear epitopes, discontinuous epitopes, or conformational epitopes of such proteins or protein fragments, either as present on the protein in its native conformation or, in some cases, as present on the proteins as denatured, as, *e.g.*, by solubilization in SDS. New epitopes may be also due to a difference in post translational modifications (PTMs) in disease versus normal tissue. For example, a particular site on a OSP may be glycosylated in cancerous cells, but not glycosylated in normal cells or vis versa. In addition, alternative splice forms of a

OSP may be indicative of cancer. Differential degradation of the C or N-terminus of a OSP may also be a marker or target for anticancer therapy. For example, an OSP may be N-terminal degraded in cancer cells exposing new epitopes to which antibodies may selectively bind for diagnostic or therapeutic uses.

As is well known in the art, the degree to which an antibody can discriminate as among molecular species in a mixture will depend, in part, upon the conformational relatedness of the species in the mixture; typically, the antibodies of the present invention will discriminate over adventitious binding to non-OSP polypeptides by at least two-fold, more typically by at least 5-fold, typically by more than 10-fold, 25-fold, 50-fold, 75-fold, and often by more than 100-fold, and on occasion by more than 500-fold or 1000-fold. When used to detect the proteins or protein fragments of the present invention, the antibody of the present invention is sufficiently specific when it can be used to determine the presence of the polypeptide of the present invention in samples derived from human ovarian.

Typically, the affinity or avidity of an antibody (or antibody multimer, as in the case of an IgM pentamer) of the present invention for a protein or protein fragment of the present invention will be at least about 1×10^{-6} molar (M), typically at least about 5×10^{-7} M, 1×10^{-7} M, with affinities and avidities of at least 1×10^{-8} M, 5×10^{-9} M, 1×10^{-10} M and up to 1×10^{-13} M proving especially useful.

The antibodies of the present invention can be naturally occurring forms, such as IgG, IgM, IgD, IgE, IgY, and IgA, from any avian, reptilian, or mammalian species.

Human antibodies can, but will infrequently, be drawn directly from human donors or human cells. In such case, antibodies to the polypeptides of the present invention will typically have resulted from fortuitous immunization, such as autoimmune immunization, with the polypeptide of the present invention. Such antibodies will typically, but will not invariably, be polyclonal. In addition, individual polyclonal antibodies may be isolated and cloned to generate monoclonals.

Human antibodies are more frequently obtained using transgenic animals that express human immunoglobulin genes, which transgenic animals can be affirmatively immunized with the protein immunogen of the present invention. Human Ig-transgenic mice capable of producing human antibodies and methods of producing human antibodies therefrom upon specific immunization are described, *inter alia*, in U.S. Patent Nos. 6,162,963; 6,150,584; 6,114,598; 6,075,181; 5,939,598; 5,877,397; 5,874,299; 5,814,318;

5,789,650; 5,770,429; 5,661,016; 5,633,425; 5,625,126; 5,569,825; 5,545,807; 5,545,806, and 5,591,669, the disclosures of which are incorporated herein by reference in their entireties. Such antibodies are typically monoclonal, and are typically produced using techniques developed for production of murine antibodies.

Human antibodies are particularly useful, and often preferred, when the antibodies of the present invention are to be administered to human beings as *in vivo* diagnostic or therapeutic agents, since recipient immune response to the administered antibody will often be substantially less than that occasioned by administration of an antibody derived from another species, such as mouse.

IgG, IgM, IgD, IgE, IgY, and IgA antibodies of the present invention are also usefully obtained from other species, including mammals such as rodents (typically mouse, but also rat, guinea pig, and hamster), lagomorphs (typically rabbits), and also larger mammals, such as sheep, goats, cows, and horses; or egg laying birds or reptiles such as chickens or alligators. In such cases, as with the transgenic human-antibody-producing non-human mammals, fortuitous immunization is not required, and the non-human mammal is typically affirmatively immunized, according to standard immunization protocols, with the polypeptide of the present invention. One form of avian antibodies may be generated using techniques described in WO 00/29444, published 25 May 2000.

As discussed above, virtually all fragments of 8 or more contiguous amino acids of a polypeptide of the present invention can be used effectively as immunogens when conjugated to a carrier, typically a protein such as bovine thyroglobulin, keyhole limpet hemocyanin, or bovine serum albumin, conveniently using a bifunctional linker such as those described elsewhere above, which discussion is incorporated by reference here.

Immunogenicity can also be conferred by fusion of the polypeptide of the present invention to other moieties. For example, polypeptides of the present invention can be produced by solid phase synthesis on a branched polylysine core matrix; these multiple antigenic peptides (MAPs) provide high purity, increased avidity, accurate chemical definition and improved safety in vaccine development. Tam *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 5409-5413 (1988); Posnett *et al.*, *J. Biol. Chem.* 263: 1719-1725 (1988).

Protocols for immunizing non-human mammals or avian species are well-established in the art. *See* Harlow *et al.* (eds.), Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory (1998); Coligan *et al.* (eds.), Current Protocols in Immunology, John Wiley & Sons, Inc. (2001); Zola, Monoclonal Antibodies: Preparation

and Use of Monoclonal Antibodies and Engineered Antibody Derivatives (Basics: From Background to Bench), Springer Verlag (2000); Gross M, Speck *J.Dtsch. Tierarztl. Wochenschr.* 103: 417-422 (1996). Immunization protocols often include multiple immunizations, either with or without adjuvants such as Freund's complete adjuvant and Freund's incomplete adjuvant, and may include naked DNA immunization (Moss, *Semin. Immunol.* 2: 317-327 (1990).

Antibodies from non-human mammals and avian species can be polyclonal or monoclonal, with polyclonal antibodies having certain advantages in immunohistochemical detection of the polypeptides of the present invention and monoclonal antibodies having advantages in identifying and distinguishing particular epitopes of the polypeptides of the present invention. Antibodies from avian species may have particular advantage in detection of the polypeptides of the present invention, in human serum or tissues (Vikinge et al., *Biosens. Bioelectron.* 13: 1257-1262 (1998). Following immunization, the antibodies of the present invention can be obtained using any art-accepted technique. Such techniques are well known in the art and are described in detail in references such as Coligan, *supra*; Zola, *supra*; Howard *et al.* (eds.), Basic Methods in Antibody Production and Characterization, CRC Press (2000); Harlow, *supra*; Davis (ed.), Monoclonal Antibody Protocols, Vol. 45, Humana Press (1995); Delves (ed.), Antibody Production: Essential Techniques, John Wiley & Son Ltd (1997); and Kenney, Antibody Solution: An Antibody Methods Manual, Chapman & Hall (1997).

Briefly, such techniques include, *inter alia*, production of monoclonal antibodies by hybridomas and expression of antibodies or fragments or derivatives thereof from host cells engineered to express immunoglobulin genes or fragments thereof. These two methods of production are not mutually exclusive: genes encoding antibodies specific for the polypeptides of the present invention can be cloned from hybridomas and thereafter expressed in other host cells. Nor need the two necessarily be performed together: *e.g.*, genes encoding antibodies specific for the polypeptides of the present invention can be cloned directly from B cells known to be specific for the desired protein, as further described in U.S. Patent No. 5,627,052, the disclosure of which is incorporated herein by reference in its entirety, or from antibody-displaying phage.

Recombinant expression in host cells is particularly useful when fragments or derivatives of the antibodies of the present invention are desired.

Host cells for recombinant antibody production of whole antibodies, antibody fragments, or antibody derivatives can be prokaryotic or eukaryotic.

Prokaryotic hosts are particularly useful for producing phage displayed antibodies of the present invention.

The technology of phage-displayed antibodies, in which antibody variable region fragments are fused, for example, to the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13, is by now well-established. *See, e.g.,* Sidhu, *Curr. Opin. Biotechnol.* 11(6): 610-6 (2000); Griffiths *et al.*, *Curr. Opin. Biotechnol.* 9(1): 102-8 (1998); Hoogenboom *et al.*, *Immunotechnology*, 4(1): 1-20 (1998); Rader *et al.*, *Current Opinion in Biotechnology* 8: 503-508 (1997); Aujame *et al.*, *Human Antibodies* 8: 155-168 (1997); Hoogenboom, *Trends in Biotechnol.* 15: 62-70 (1997); de Kruif *et al.*, 17: 453-455 (1996); Barbas *et al.*, *Trends in Biotechnol.* 14: 230-234 (1996); Winter *et al.*, *Ann. Rev. Immunol.* 433-455 (1994). Techniques and protocols required to generate, propagate, screen (pan), and use the antibody fragments from such libraries have recently been compiled. *See, e.g.,* Barbas (2001), *supra*; Kay, *supra*; and Abelson, *supra*.

Typically, phage-displayed antibody fragments are scFv fragments or Fab fragments; when desired, full length antibodies can be produced by cloning the variable regions from the displaying phage into a complete antibody and expressing the full length antibody in a further prokaryotic or a eukaryotic host cell. Eukaryotic cells are also useful for expression of the antibodies, antibody fragments, and antibody derivatives of the present invention. For example, antibody fragments of the present invention can be produced in *Pichia pastoris* and in *Saccharomyces cerevisiae*. *See, e.g.,* Takahashi *et al.*, *Biosci. Biotechnol. Biochem.* 64(10): 2138-44 (2000); Freyre *et al.*, J. Biotechnol. 76(2-3):1 57-63 (2000); Fischer *et al.*, *Biotechnol. Appl. Biochem.* 30 (Pt 2): 117-20 (1999); Pennell *et al.*, *Res. Immunol.* 149(6): 599-603 (1998); Eldin *et al.*, *J. Immunol. Methods.* 201(1): 67-75 (1997);, Frenken *et al.*, *Res. Immunol.* 149(6): 589-99 (1998); and Shusta *et al.*, *Nature Biotechnol.* 16(8): 773-7 (1998).

Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in insect cells. *See, e.g.,* Li *et al.*, *Protein Expr. Purif.* 21(1): 121-8 (2001); Ailor *et al.*, *Biotechnol. Bioeng.* 58(2-3): 196-203 (1998); Hsu *et al.*, *Biotechnol. Prog.* 13(1): 96-104 (1997); Edelman *et al.*, *Immunology* 91(1): 13-9 (1997); and Nesbit *et al.*, *J. Immunol. Methods* 151(1-2): 201-8 (1992).

Antibodies and fragments and derivatives thereof of the present invention can also be produced in plant cells, particularly maize or tobacco, Giddings *et al.*, *Nature Biotechnol.* 18(11): 1151-5 (2000); Gavilondo *et al.*, *Biotechniques* 29(1): 128-38 (2000); Fischer *et al.*, *J. Biol. Regul. Homeost. Agents* 14(2): 83-92 (2000); Fischer *et al.*, *Biotechnol. Appl. Biochem.* 30 (Pt 2): 113-6 (1999); Fischer *et al.*, *Biol. Chem.* 380(7-8): 825-39 (1999); Russell, *Curr. Top. Microbiol. Immunol.* 240: 119-38 (1999); and Ma *et al.*, *Plant Physiol.* 109(2): 341-6 (1995).

Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in transgenic, non-human, mammalian milk. *See, e.g.* Pollock et al., *J. Immunol Methods.* 231: 147-57 (1999); Young et al., *Res. Immunol.* 149: 609-10 (1998); and Limonta et al., *Immunotechnology* 1: 107-13 (1995).

Mammalian cells useful for recombinant expression of antibodies, antibody fragments, and antibody derivatives of the present invention include CHO cells, COS cells, 293 cells, and myeloma cells. Verma *et al.*, *J. Immunol. Methods* 216(1-2):165-81 (1998) review and compare bacterial, yeast, insect and mammalian expression systems for expression of antibodies. Antibodies of the present invention can also be prepared by cell free translation, as further described in Merk *et al.*, *J. Biochem.* (Tokyo) 125(2): 328-33 (1999) and Ryabova *et al.*, *Nature Biotechnol.* 15(1): 79-84 (1997), and in the milk of transgenic animals, as further described in Pollock *et al.*, *J. Immunol. Methods* 231(1-2): 147-57 (1999).

The invention further provides antibody fragments that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention. Among such useful fragments are Fab, Fab', Fv, $F(ab)'_2$, and single chain Fv (scFv) fragments. Other useful fragments are described in Hudson, *Curr. Opin. Biotechnol.* 9(4): 395-402 (1998).

The present invention also relates to antibody derivatives that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of

the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention.

Among such useful derivatives are chimeric, primatized, and humanized antibodies; such derivatives are less immunogenic in human beings, and thus are more suitable for *in vivo* administration, than are unmodified antibodies from non-human mammalian species. Another useful method is PEGylation to increase the serum half life of the antibodies.

Chimeric antibodies typically include heavy and/or light chain variable regions (including both CDR and framework residues) of immunoglobulins of one species, typically mouse, fused to constant regions of another species, typically human. *See, e.g.*, Morrison *et al.*, *Proc. Natl. Acad. Sci USA*.81(21): 6851-5 (1984); Sharon *et al.*, *Nature* 309(5966): 364-7 (1984); Takeda *et al.*, *Nature* 314(6010): 452-4 (1985); and U.S. Patent No. 5,807,715 the disclosure of which is incorporated herein by reference in its entirety. Primatized and humanized antibodies typically include heavy and/or light chain CDRs from a murine antibody grafted into a non-human primate or human antibody V region framework, usually further comprising a human constant region, Riechmann *et al.*, *Nature* 332(6162): 323-7 (1988); Co *et al.*, *Nature* 351(6326): 501-2 (1991); and U.S. Patent Nos. 6,054,297; 5,821,337; 5,770,196; 5,766,886; 5,821,123; 5,869,619; 6,180,377; 6,013,256; 5,693,761; and 6,180,370, the disclosures of which are incorporated herein by reference in their entireties. Other useful antibody derivatives of the invention include heteromeric antibody complexes and antibody fusions, such as diabodies (bispecific antibodies), single-chain diabodies, and intrabodies.

It is contemplated that the nucleic acids encoding the antibodies of the present invention can be operably joined to other nucleic acids forming a recombinant vector for cloning or for expression of the antibodies of the invention. Accordingly, the present invention includes any recombinant vector containing the coding sequences, or part thereof, whether for eukaryotic transduction, transfection or gene therapy. Such vectors may be prepared using conventional molecular biology techniques, known to those with skill in the art, and would comprise DNA encoding sequences for the immunoglobulin V-regions including framework and CDRs or parts thereof, and a suitable promoter either with or without a signal sequence for intracellular transport. Such vectors may be transduced or transfected into eukaryotic cells or used for gene therapy (Marasco et al., *Proc. Natl. Acad. Sci. (USA)* 90: 7889-7893 (1993); Duan et al., *Proc. Natl. Acad. Sci.*

(USA) 91: 5075-5079 (1994), by conventional techniques, known to those with skill in the art.

The antibodies of the present invention, including fragments and derivatives thereof, can usefully be labeled. It is, therefore, another aspect of the present invention to provide labeled antibodies that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention. The choice of label depends, in part, upon the desired use.

For example, when the antibodies of the present invention are used for immunohistochemical staining of tissue samples, the label can usefully be an enzyme that catalyzes production and local deposition of a detectable product. Enzymes typically conjugated to antibodies to permit their immunohistochemical visualization are well known, and include alkaline phosphatase, β-galactosidase, glucose oxidase, horseradish peroxidase (HRP), and urease. Typical substrates for production and deposition of visually detectable products include o-nitrophenyl-beta-D-galactopyranoside (ONPG); o-phenylenediamine dihydrochloride (OPD); p-nitrophenyl phosphate (PNPP); p-nitrophenyl-beta-D-galactopryanoside (PNPG); 3',3'-diaminobenzidine (DAB); 3-amino-9-ethylcarbazole (AEC); 4-chloro-1-naphthol (CN); 5-bromo-4-chloro-3-indolyl-phosphate (BCIP); ABTS®; BluoGal; iodonitrotetrazolium (INT); nitroblue tetrazolium chloride (NBT); phenazine methosulfate (PMS); phenolphthalein monophosphate (PMP); tetramethyl benzidine (TMB); tetranitroblue tetrazolium (TNBT); X-Gal; X-Gluc; and X-Glucoside.

Other substrates can be used to produce products for local deposition that are luminescent. For example, in the presence of hydrogen peroxide (H_2O_2), horseradish peroxidase (HRP) can catalyze the oxidation of cyclic diacylhydrazides, such as luminol. Immediately following the oxidation, the luminol is in an excited state (intermediate reaction product), which decays to the ground state by emitting light. Strong enhancement of the light emission is produced by enhancers, such as phenolic compounds. Advantages include high sensitivity, high resolution, and rapid detection without radioactivity and requiring only small amounts of antibody. *See, e.g.*, Thorpe *et al.*, *Methods Enzymol.* 133: 331-53 (1986); Kricka *et al.*, *J. Immunoassay* 17(1): 67-83 (1996); and Lundqvist *et al.*, *J.*

Biolumin. Chemilumin. 10(6): 353-9 (1995). Kits for such enhanced chemiluminescent detection (ECL) are available commercially. The antibodies can also be labeled using colloidal gold.

As another example, when the antibodies of the present invention are used, *e.g.*, for flow cytometric detection, for scanning laser cytometric detection, or for fluorescent immunoassay, they can usefully be labeled with fluorophores. There are a wide variety of fluorophore labels that can usefully be attached to the antibodies of the present invention. For flow cytometric applications, both for extracellular detection and for intracellular detection, common useful fluorophores can be fluorescein isothiocyanate (FITC), allophycocyanin (APC), R-phycoerythrin (PE), peridinin chlorophyll protein (PerCP), Texas Red, Cy3, Cy5, fluorescence resonance energy tandem fluorophores such as PerCP-Cy5.5, PE-Cy5, PE-Cy5.5, PE-Cy7, PE-Texas Red, and APC-Cy7.

Other fluorophores include, *inter alia*, Alexa Fluor® 350, Alexa Fluor® 488, Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from Molecular Probes, Inc., Eugene, OR, USA), and Cy2, Cy3, Cy3.5, Cy5, Cy5.5, Cy7, all of which are also useful for fluorescently labeling the antibodies of the present invention. For secondary detection using labeled avidin, streptavidin, captavidin or neutravidin, the antibodies of the present invention can usefully be labeled with biotin.

When the antibodies of the present invention are used, *e.g.*, for western blotting applications, they can usefully be labeled with radioisotopes, such as ^{33}P, ^{32}P, ^{35}S, ^{3}H, and ^{125}I. As another example, when the antibodies of the present invention are used for radioimmunotherapy, the label can usefully be ^{228}Th, ^{227}Ac, ^{225}Ac, ^{223}Ra, ^{213}Bi, ^{212}Pb, ^{212}Bi, ^{211}At, ^{203}Pb, ^{194}Os, ^{188}Re, ^{186}Re, ^{153}Sm, ^{149}Tb, ^{131}I, ^{125}I, ^{111}In, ^{105}Rh, ^{99m}Tc, ^{97}Ru, ^{90}Y, ^{90}Sr, ^{88}Y, ^{72}Se, ^{67}Cu, or ^{47}Sc.

As another example, when the antibodies of the present invention are to be used for *in vivo* diagnostic use, they can be rendered detectable by conjugation to MRI contrast

agents, such as gadolinium diethylenetriaminepentaacetic acid (DTPA), Lauffer *et al.*, *Radiology* 207(2): 529-38 (1998), or by radioisotopic labeling.

As would be understood, use of the labels described above is not restricted to the application as for which they were mentioned.

The antibodies of the present invention, including fragments and derivatives thereof, can also be conjugated to toxins, in order to target the toxin's ablative action to cells that display and/or express the polypeptides of the present invention. Commonly, the antibody in such immunotoxins is conjugated to Pseudomonas exotoxin A, diphtheria toxin, shiga toxin A, anthrax toxin lethal factor, or ricin. *See* Hall (ed.), Immunotoxin Methods and Protocols (Methods in Molecular Biology, vol. 166), Humana Press (2000); and Frankel *et al.* (eds.), Clinical Applications of Immunotoxins, Springer-Verlag (1998).

The antibodies of the present invention can usefully be attached to a substrate, and it is, therefore, another aspect of the invention to provide antibodies that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, attached to a substrate. Substrates can be porous or nonporous, planar or nonplanar. For example, the antibodies of the present invention can usefully be conjugated to filtration media, such as NHS-activated Sepharose or CNBr-activated Sepharose for purposes of immunoaffinity chromatography. For example, the antibodies of the present invention can usefully be attached to paramagnetic microspheres, typically by biotin-streptavidin interaction, which microsphere can then be used for isolation of cells that express or display the polypeptides of the present invention. As another example, the antibodies of the present invention can usefully be attached to the surface of a microtiter plate for ELISA.

As noted above, the antibodies of the present invention can be produced in prokaryotic and eukaryotic cells. It is, therefore, another aspect of the present invention to provide cells that express the antibodies of the present invention, including hybridoma cells, B cells, plasma cells, and host cells recombinantly modified to express the antibodies of the present invention.

In yet a further aspect, the present invention provides aptamers evolved to bind specifically to one or more of the OSPs of the present invention or to polypeptides encoded by the OSNAs of the invention.

In sum, one of skill in the art, provided with the teachings of this invention, has available a variety of methods which may be used to alter the biological properties of the antibodies of this invention including methods which would increase or decrease the stability or half-life, immunogenicity, toxicity, affinity or yield of a given antibody molecule, or to alter it in any other way that may render it more suitable for a particular application.

Transgenic Animals and Cells

In another aspect, the invention provides transgenic cells and non-human organisms comprising nucleic acid molecules of the invention. In a preferred embodiment, the transgenic cells and non-human organisms comprise a nucleic acid molecule encoding a OSP. In a preferred embodiment, the OSP comprises an amino acid sequence selected from SEQ ID NO: 249-396, or a fragment, mutein, homologous protein or allelic variant thereof. In another preferred embodiment, the transgenic cells and non-human organism comprise a OSNA of the invention, preferably a OSNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-248, or a part, substantially similar nucleic acid molecule, allelic variant or hybridizing nucleic acid molecule thereof.

In another embodiment, the transgenic cells and non-human organisms have a targeted disruption or replacement of the endogenous orthologue of the human OSG. The transgenic cells can be embryonic stem cells or somatic cells. The transgenic non-human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes. Methods of producing transgenic animals are well known in the art. *See, e.g.*, Hogan *et al.*, Manipulating the Mouse Embryo: A Laboratory Manual, 2d ed., Cold Spring Harbor Press (1999); Jackson *et al.*, Mouse Genetics and Transgenics: A Practical Approach, Oxford University Press (2000); and Pinkert, Transgenic Animal Technology: A Laboratory Handbook, Academic Press (1999).

Any technique known in the art may be used to introduce a nucleic acid molecule of the invention into an animal to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection. (*see, e.g.*, Paterson

et al., *Appl. Microbiol. Biotechnol.* 40: 691-698 (1994); Carver *et al.*, *Biotechnology* 11: 1263-1270 (1993); Wright *et al.*, *Biotechnology* 9: 830-834 (1991); and U.S. Patent No. 4,873,191, herein incorporated by reference in its entirety); retrovirus-mediated gene transfer into germ lines, blastocysts or embryos (*see, e.g.,* Van der Putten *et al.*, *Proc. Natl. Acad. Sci., USA* 82: 6148-6152 (1985)); gene targeting in embryonic stem cells (*see, e.g.,* Thompson *et al.*, *Cell* 56: 313-321 (1989)); electroporation of cells or embryos (*see, e.g.,* Lo, 1983, *Mol. Cell. Biol.* 3: 1803-1814 (1983)); introduction using a gene gun (*see, e.g.*, Ulmer *et al.*, *Science* 259: 1745-49 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (*see, e.g.,* Lavitrano *et al.*, *Cell* 57: 717-723 (1989)).

Other techniques include, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (*see, e.g.,* Campell *et al.*, *Nature* 380: 64-66 (1996); Wilmut *et al.*, *Nature* 385: 810-813 (1997)). The present invention provides for transgenic animals that carry the transgene (*i.e.*, a nucleic acid molecule of the invention) in all their cells, as well as animals which carry the transgene in some, but not all their cells, i.e. e., mosaic animals or chimeric animals.

The transgene may be integrated as a single transgene or as multiple copies, such as in concatamers, e. g., head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, *e.g.*, the teaching of Lasko *et al. et al.*, *Proc. Natl. Acad. Sci. USA* 89: 6232- 6236 (1992). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (RT-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Methods for creating a transgenic animal with a disruption of a targeted gene are also well known in the art. In general, a vector is designed to comprise some nucleotide sequences homologous to the endogenous targeted gene. The vector is introduced into a cell so that it may integrate, via homologous recombination with chromosomal sequences, into the endogenous gene, thereby disrupting the function of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type. *See, e.g.,* Gu *et al.*, *Science* 265: 103-106 (1994). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. *See, e.g.*, Smithies *et al.*, *Nature* 317: 230-234 (1985); Thomas *et al.*, *Cell* 51: 503-512 (1987); Thompson *et al.*, *Cell* 5: 313-321 (1989).

In one embodiment, a mutant, non-functional nucleic acid molecule of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous nucleic acid sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention in vivo. In another embodiment, techniques known in the art are used to generate knockouts in cells that

contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene. *See, e.g.,* Thomas, *supra* and Thompson, *supra*. However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site in vivo using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient in vivo. Such cells may be obtained from an animal or patient or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered in vitro using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. *See, e.g.,* U.S. Patent Nos. 5,399,349 and 5,460,959, each of which is incorporated by reference herein in its entirety.

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the

development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Computer Readable Means

A further aspect of the invention is a computer readable means for storing the nucleic acid and amino acid sequences of the instant invention. In a preferred embodiment, the invention provides a computer readable means for storing SEQ ID NO: 249-396 and SEQ ID NO: 1-248 as described herein, as the complete set of sequences or in any combination. The records of the computer readable means can be accessed for reading and display and for interface with a computer system for the application of programs allowing for the location of data upon a query for data meeting certain criteria, the comparison of sequences, the alignment or ordering of sequences meeting a set of criteria, and the like.

The nucleic acid and amino acid sequences of the invention are particularly useful as components in databases useful for search analyses as well as in sequence analysis algorithms. As used herein, the terms "nucleic acid sequences of the invention" and "amino acid sequences of the invention" mean any detectable chemical or physical characteristic of a polynucleotide or polypeptide of the invention that is or may be reduced to or stored in a computer readable form. These include, without limitation, chromatographic scan data or peak data, photographic data or scan data therefrom, and mass spectrographic data.

This invention provides computer readable media having stored thereon sequences of the invention. A computer readable medium may comprise one or more of the following: a nucleic acid sequence comprising a sequence of a nucleic acid sequence of the invention; an amino acid sequence comprising an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said sequences comprises

the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set representing a nucleic acid sequence comprising the sequence of one or more nucleic acid sequences of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said sequences comprises the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set representing a nucleic acid sequence comprising the sequence of a nucleic acid sequence of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention. The computer readable medium can be any composition of matter used to store information or data, including, for example, commercially available floppy disks, tapes, hard drives, compact disks, and video disks.

Also provided by the invention are methods for the analysis of character sequences, particularly genetic sequences. Preferred methods of sequence analysis include, for example, methods of sequence homology analysis, such as identity and similarity analysis, RNA structure analysis, sequence assembly, cladistic analysis, sequence motif analysis, open reading frame determination, nucleic acid base calling, and sequencing chromatogram peak analysis.

A computer-based method is provided for performing nucleic acid sequence identity or similarity identification. This method comprises the steps of providing a nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and comparing said nucleic acid sequence to at least one nucleic acid or amino acid sequence to identify sequence identity or similarity.

A computer-based method is also provided for performing amino acid homology identification, said method comprising the steps of: providing an amino acid sequence comprising the sequence of an amino acid of the invention in a computer readable medium; and comparing said amino acid sequence to at least one nucleic acid or an amino acid sequence to identify homology.

A computer-based method is still further provided for assembly of overlapping nucleic acid sequences into a single nucleic acid sequence, said method comprising the steps of: providing a first nucleic acid sequence comprising the sequence of a nucleic acid

of the invention in a computer readable medium; and screening for at least one overlapping region between said first nucleic acid sequence and a second nucleic acid sequence. In addition, the invention includes a method of using patterns of expression associated with either the nucleic acids or proteins in a computer-based method to diagnose disease.

Diagnostic Methods for ovarian Cancer

The present invention also relates to quantitative and qualitative diagnostic assays and methods for detecting, diagnosing, monitoring, staging and predicting cancers by comparing expression of a OSNA or a OSP in a human patient that has or may have ovarian cancer, or who is at risk of developing ovarian cancer, with the expression of a OSNA or a OSP in a normal human control. For purposes of the present invention, "expression of a OSNA" or "OSNA expression" means the quantity of OSNA mRNA that can be measured by any method known in the art or the level of transcription that can be measured by any method known in the art in a cell, tissue, organ or whole patient. Similarly, the term "expression of a OSP" or "OSP expression" means the amount of OSP that can be measured by any method known in the art or the level of translation of a OSNA that can be measured by any method known in the art.

The present invention provides methods for diagnosing ovarian cancer in a patient, by analyzing for changes in levels of OSNA or OSP in cells, tissues, organs or bodily fluids compared with levels of OSNA or OSP in cells, tissues, organs or bodily fluids of preferably the same type from a normal human control, wherein an increase, or decrease in certain cases, in levels of a OSNA or OSP in the patient versus the normal human control is associated with the presence of ovarian cancer or with a predilection to the disease. In another preferred embodiment, the present invention provides methods for diagnosing ovarian cancer in a patient by analyzing changes in the structure of the mRNA of a OSG compared to the mRNA from a normal control. These changes include, without limitation, aberrant splicing, alterations in polyadenylation and/or alterations in 5' nucleotide capping. In yet another preferred embodiment, the present invention provides methods for diagnosing ovarian cancer in a patient by analyzing changes in a OSP compared to a OSP from a normal patient. These changes include, *e.g.*, alterations, including post translational modifications such as glycosylation and/or phosphorylation of the OSP or changes in the subcellular OSP localization.

For purposes of the present invention, diagnosing means that OSNA or OSP levels are used to determine the presence or absence of disease in a patient. As will be understood by those of skill in the art, measurement of other diagnostic parameters may be required for definitive diagnosis or determination of the appropriate treatment for the disease. The determination may be made by a clinician, a doctor, a testing laboratory, or a patient using an over the counter test. The patient may have symptoms of disease or may be asymptomatic. In addition, the OSNA or OSP levels of the present invention may be used as screening marker to determine whether further tests or biopsies are warranted. In addition, the OSNA or OSP levels may be used to determine the vulnerability or susceptibility to disease.

In a preferred embodiment, the expression of a OSNA is measured by determining the amount of a mRNA that encodes an amino acid sequence selected from SEQ ID NO: 249-396, a homolog, an allelic variant, or a fragment thereof. In a more preferred embodiment, the OSNA expression that is measured is the level of expression of a OSNA mRNA selected from SEQ ID NO: 1-248, or a hybridizing nucleic acid, homologous nucleic acid or allelic variant thereof, or a part of any of these nucleic acid molecules. OSNA expression may be measured by any method known in the art, such as those described *supra*, including measuring mRNA expression by Northern blot, quantitative or qualitative reverse transcriptase PCR (RT-PCR), microarray, dot or slot blots or *in situ* hybridization. *See, e.g.*, Ausubel (1992), *supra*; Ausubel (1999), *supra*; Sambrook (1989), *supra*; and Sambrook (2001), *supra*. OSNA transcription may be measured by any method known in the art including using a reporter gene hooked up to the promoter of a OSG of interest or doing nuclear run-off assays. Alterations in mRNA structure, *e.g.*, aberrant splicing variants, may be determined by any method known in the art, including, RT-PCR followed by sequencing or restriction analysis. As necessary, OSNA expression may be compared to a known control, such as normal ovarian nucleic acid, to detect a change in expression.

In another preferred embodiment, the expression of a OSP is measured by determining the level of a OSP having an amino acid sequence selected from the group consisting of SEQ ID NO: 249-396, a homolog, an allelic variant, or a fragment thereof. Such levels are preferably determined in at least one of cells, tissues, organs and/or bodily fluids, including determination of normal and abnormal levels. Thus, for instance, a diagnostic assay in accordance with the invention for diagnosing over- or underexpression

of a OSNA or OSP compared to normal control bodily fluids, cells, or tissue samples may be used to diagnose the presence of ovarian cancer. The expression level of a OSP may be determined by any method known in the art, such as those described *supra*. In a preferred embodiment, the OSP expression level may be determined by radioimmunoassays, competitive-binding assays, ELISA, Western blot, FACS, immunohistochemistry, immunoprecipitation, proteomic approaches: two-dimensional gel electrophoresis (2D electrophoresis) and non-gel-based approaches such as mass spectrometry or protein interaction profiling. *See*, e.g, Harlow (1999), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. Alterations in the OSP structure may be determined by any method known in the art, including, *e.g.*, using antibodies that specifically recognize phosphoserine, phosphothreonine or phosphotyrosine residues, two-dimensional polyacrylamide gel electrophoresis (2D PAGE) and/or chemical analysis of amino acid residues of the protein. *Id.*

In a preferred embodiment, a radioimmunoassay (RIA) or an ELISA is used. An antibody specific to a OSP is prepared if one is not already available. In a preferred embodiment, the antibody is a monoclonal antibody. The anti-OSP antibody is bound to a solid support and any free protein binding sites on the solid support are blocked with a protein such as bovine serum albumin. A sample of interest is incubated with the antibody on the solid support under conditions in which the OSP will bind to the anti-OSP antibody. The sample is removed, the solid support is washed to remove unbound material, and an anti-OSP antibody that is linked to a detectable reagent (a radioactive substance for RIA and an enzyme for ELISA) is added to the solid support and incubated under conditions in which binding of the OSP to the labeled antibody will occur. After binding, the unbound labeled antibody is removed by washing. For an ELISA, one or more substrates are added to produce a colored reaction product that is based upon the amount of an OSP in the sample. For an RIA, the solid support is counted for radioactive decay signals by any method known in the art. Quantitative results for both RIA and ELISA typically are obtained by reference to a standard curve.

Other methods to measure OSP levels are known in the art. For instance, a competition assay may be employed wherein an anti-OSP antibody is attached to a solid support and an allocated amount of a labeled OSP and a sample of interest are incubated with the solid support. The amount of labeled OSP attached to the solid support can be correlated to the quantity of a OSP in the sample.

Of the proteomic approaches, 2D PAGE is a well known technique. Isolation of individual proteins from a sample such as serum is accomplished using sequential separation of proteins by isoelectric point and molecular weight. Typically, polypeptides are first separated by isoelectric point (the first dimension) and then separated by size using an electric current (the second dimension). In general, the second dimension is perpendicular to the first dimension. Because no two proteins with different sequences are identical on the basis of both size and charge, the result of 2D PAGE is a roughly square gel in which each protein occupies a unique spot. Analysis of the spots with chemical or antibody probes, or subsequent protein microsequencing can reveal the relative abundance of a given protein and the identity of the proteins in the sample.

Expression levels of a OSNA can be determined by any method known in the art, including PCR and other nucleic acid methods, such as ligase chain reaction (LCR) and nucleic acid sequence based amplification (NASBA), can be used to detect malignant cells for diagnosis and monitoring of various malignancies. For example, reverse-transcriptase PCR (RT-PCR) is a powerful technique which can be used to detect the presence of a specific mRNA population in a complex mixture of thousands of other mRNA species. In RT-PCR, an mRNA species is first reverse transcribed to complementary DNA (cDNA) with use of the enzyme reverse transcriptase; the cDNA is then amplified as in a standard PCR reaction.

Hybridization to specific DNA molecules (*e.g.*, oligonucleotides) arrayed on a solid support can be used to both detect the expression of and quantitate the level of expression of one or more OSNAs of interest. In this approach, all or a portion of one or more OSNAs is fixed to a substrate. A sample of interest, which may comprise RNA, *e.g.*, total RNA or polyA-selected mRNA, or a complementary DNA (cDNA) copy of the RNA is incubated with the solid support under conditions in which hybridization will occur between the DNA on the solid support and the nucleic acid molecules in the sample of interest. Hybridization between the substrate-bound DNA and the nucleic acid molecules in the sample can be detected and quantitated by several means, including, without limitation, radioactive labeling or fluorescent labeling of the nucleic acid molecule or a secondary molecule designed to detect the hybrid.

The above tests can be carried out on samples derived from a variety of cells, bodily fluids and/or tissue extracts such as homogenates or solubilized tissue obtained from a patient. Tissue extracts are obtained routinely from tissue biopsy and autopsy

material. Bodily fluids useful in the present invention include blood, urine, saliva or any other bodily secretion or derivative thereof. As used herein "blood" includes whole blood, plasma, serum, circulating epithelial cells, constituents, or any derivative of blood.

In addition to detection in bodily fluids, the proteins and nucleic acids of the invention are suitable to detection by cell capture technology. Whole cells may be captured by a variety methods for example magnetic separation, U.S. Patent. Nos. 5,200,084; 5,186,827; 5,108,933; 4,925,788, the disclosures of which are incorporated herein by reference in their entireties. Epithelial cells may be captured using such products as Dynabeads® or CELLection™ (Dynal Biotech, Oslo, Norway). Alternatively, fractions of blood may be captured, e.g., the buffy coat fraction (50mm cells isolated from 5ml of blood) containing epithelial cells. In addition, cancer cells may be captured using the techniques described in WO 00/47998, the disclosure of which is incorporated herein by reference in its entirety. Once the cells are captured or concentrated, the proteins or nucleic acids are detected by the means described in the subject application. Alternatively, nucleic acids may be captured directly from blood samples, see U.S. Patent Nos. 6,156,504, 5,501,963; or WO 01/42504 , the disclosures of which are incorporated herein by reference in their entireties.

In a preferred embodiment, the specimen tested for expression of OSNA or OSP includes without limitation ovarian tissue, ovarian cells grown in cell culture, blood, serum, lymph node tissue, and lymphatic fluid. In another preferred embodiment, especially when metastasis of a primary ovarian cancer is known or suspected, specimens include, without limitation, tissues from brain, bone, bone marrow, liver, lungs, colon, and adrenal glands. In general, the tissues may be sampled by biopsy, including, without limitation, needle biopsy, *e.g.*, transthoracic needle aspiration, cervical mediatinoscopy, endoscopic lymph node biopsy, video-assisted thoracoscopy, exploratory thoracotomy, bone marrow biopsy and bone marrow aspiration.

All the methods of the present invention may optionally include determining the expression levels of one or more other cancer markers in addition to determining the expression level of a OSNA or OSP. In many cases, the use of another cancer marker will decrease the likelihood of false positives or false negatives. In one embodiment, the one or more other cancer markers include other OSNA or OSPs as disclosed herein. Other cancer markers useful in the present invention will depend on the cancer being tested and are known to those of skill in the art. In a preferred embodiment, at least one other cancer

marker in addition to a particular OSNA or OSP is measured. In a more preferred embodiment, at least two other additional cancer markers are used. In an even more preferred embodiment, at least three, more preferably at least five, even more preferably at least ten additional cancer markers are used.

Diagnosing

In one aspect, the invention provides a method for determining the expression levels and/or structural alterations of one or more OSNA and/or OSP in a sample from a patient suspected of having ovarian cancer. In general, the method comprises the steps of obtaining the sample from the patient, determining the expression level or structural alterations of a OSNA and/or OSP and then ascertaining whether the patient has ovarian cancer from the expression level of the OSNA or OSP. In general, if high expression relative to a control of a OSNA or OSP is indicative of ovarian cancer, a diagnostic assay is considered positive if the level of expression of the OSNA or OSP is at least one and a half times higher, and more preferably are at least two times higher, still more preferably five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a OSNA or OSP is indicative of ovarian cancer, a diagnostic assay is considered positive if the level of expression of the OSNA or OSP is at least one and a half times lower, and more preferably are at least two times lower, still more preferably five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

The present invention also provides a method of determining whether ovarian cancer has metastasized in a patient. One may identify whether the ovarian cancer has metastasized by measuring the expression levels and/or structural alterations of one or more OSNAs and/or OSPs in a variety of tissues. The presence of a OSNA or OSP in a certain tissue at levels higher than that of corresponding noncancerous tissue (*e.g.*, the same tissue from another individual) is indicative of metastasis if high level expression of a OSNA or OSP is associated with ovarian cancer. Similarly, the presence of a OSNA or OSP in a tissue at levels lower than that of corresponding noncancerous tissue is indicative of metastasis if low level expression of a OSNA or OSP is associated with ovarian cancer.

Further, the presence of a structurally altered OSNA or OSP that is associated with ovarian cancer is also indicative of metastasis.

In general, if high expression relative to a control of a OSNA or OSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of the OSNA or OSP is at least one and a half times higher, and more preferably are at least two times higher, still more preferably five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a OSNA or OSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of the OSNA or OSP is at least one and a half times lower, and more preferably are at least two times lower, still more preferably five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control.

Staging

The invention also provides a method of staging ovarian cancer in a human patient. The method comprises identifying a human patient having ovarian cancer and analyzing cells, tissues or bodily fluids from such human patient for expression levels and/or structural alterations of one or more OSNAs or OSPs. First, one or more tumors from a variety of patients are staged according to procedures well known in the art, and the expression levels of one or more OSNAs or OSPs is determined for each stage to obtain a standard expression level for each OSNA and OSP. Then, the OSNA or OSP expression levels of the OSNA or OSP are determined in a biological sample from a patient whose stage of cancer is not known. The OSNA or OSP expression levels from the patient are then compared to the standard expression level. By comparing the expression level of the OSNAs and OSPs from the patient to the standard expression levels, one may determine the stage of the tumor. The same procedure may be followed using structural alterations of a OSNA or OSP to determine the stage of a ovarian cancer.

Monitoring

Further provided is a method of monitoring ovarian cancer in a human patient. One may monitor a human patient to determine whether there has been metastasis and, if there has been, when metastasis began to occur. One may also monitor a human patient to determine whether a preneoplastic lesion has become cancerous. One may also monitor a

human patient to determine whether a therapy, *e.g.*, chemotherapy, radiotherapy or surgery, has decreased or eliminated the ovarian cancer. The monitoring may determine if there has been a reoccurrence and, if so, determine its nature. The method comprises identifying a human patient that one wants to monitor for ovarian cancer, periodically analyzing cells, tissues or bodily fluids from such human patient for expression levels of one or more OSNAs or OSPs, and comparing the OSNA or OSP levels over time to those OSNA or OSP expression levels obtained previously. Patients may also be monitored by measuring one or more structural alterations in a OSNA or OSP that are associated with ovarian cancer.

If increased expression of a OSNA or OSP is associated with metastasis, treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting an increase in the expression level of a OSNA or OSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. One having ordinary skill in the art would recognize that if this were the case, then a decreased expression level would be indicative of no metastasis, effective therapy or failure to progress to a neoplastic lesion. If decreased expression of a OSNA or OSP is associated with metastasis, treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting a decrease in the expression level of a OSNA or OSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. In a preferred embodiment, the levels of OSNAs or OSPs are determined from the same cell type, tissue or bodily fluid as prior patient samples. Monitoring a patient for onset of ovarian cancer metastasis is periodic and preferably is done on a quarterly basis, but may be done more or less frequently.

The methods described herein can further be utilized as prognostic assays to identify subjects having or at risk of developing a disease or disorder associated with increased or decreased expression levels of a OSNA and/or OSP. The present invention provides a method in which a test sample is obtained from a human patient and one or more OSNAs and/or OSPs are detected. The presence of higher (or lower) OSNA or OSP levels as compared to normal human controls is diagnostic for the human patient being at risk for developing cancer, particularly ovarian cancer. The effectiveness of therapeutic agents to decrease (or increase) expression or activity of one or more OSNAs and/or OSPs of the invention can also be monitored by analyzing levels of expression of the OSNAs and/or OSPs in a human patient in clinical trials or in *in vitro* screening assays such as in

human cells. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the human patient or cells, as the case may be, to the agent being tested.

Detection of Genetic Lesions or Mutations

The methods of the present invention can also be used to detect genetic lesions or mutations in a OSG, thereby determining if a human with the genetic lesion is susceptible to developing ovarian cancer or to determine what genetic lesions are responsible, or are partly responsible, for a person's existing ovarian cancer. Genetic lesions can be detected, for example, by ascertaining the existence of a deletion, insertion and/or substitution of one or more nucleotides from the OSGs of this invention, a chromosomal rearrangement of a OSG, an aberrant modification of a OSG (such as of the methylation pattern of the genomic DNA), or allelic loss of a OSG. Methods to detect such lesions in the OSG of this invention are known to those having ordinary skill in the art following the teachings of the specification.

Methods of Detecting Noncancerous ovarian Diseases

The present invention also provides methods for determining the expression levels and/or structural alterations of one or more OSNAs and/or OSPs in a sample from a patient suspected of having or known to have a noncancerous ovarian disease. In general, the method comprises the steps of obtaining a sample from the patient, determining the expression level or structural alterations of a OSNA and/or OSP, comparing the expression level or structural alteration of the OSNA or OSP to a normal ovarian control, and then ascertaining whether the patient has a noncancerous ovarian disease. In general, if high expression relative to a control of a OSNA or OSP is indicative of a particular noncancerous ovarian disease, a diagnostic assay is considered positive if the level of expression of the OSNA or OSP is at least two times higher, and more preferably are at least five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a OSNA or OSP is indicative of a noncancerous ovarian disease, a diagnostic assay is considered positive if the level of expression of the OSNA or OSP is at least two times lower, more preferably are at least five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid

of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

One having ordinary skill in the art may determine whether a OSNA and/or OSP is associated with a particular noncancerous ovarian disease by obtaining ovarian tissue from a patient having a noncancerous ovarian disease of interest and determining which OSNAs and/or OSPs are expressed in the tissue at either a higher or a lower level than in normal ovarian tissue. In another embodiment, one may determine whether a OSNA or OSP exhibits structural alterations in a particular noncancerous ovarian disease state by obtaining ovarian tissue from a patient having a noncancerous ovarian disease of interest and determining the structural alterations in one or more OSNAs and/or OSPs relative to normal ovarian tissue.

Methods for Identifying ovarian Tissue

In another aspect, the invention provides methods for identifying ovarian tissue. These methods are particularly useful in, *e.g.*, forensic science, ovarian cell differentiation and development, and in tissue engineering.

In one embodiment, the invention provides a method for determining whether a sample is ovarian tissue or has ovarian tissue-like characteristics. The method comprises the steps of providing a sample suspected of comprising ovarian tissue or having ovarian tissue-like characteristics, determining whether the sample expresses one or more OSNAs and/or OSPs, and, if the sample expresses one or more OSNAs and/or OSPs, concluding that the sample comprises ovarian tissue. In a preferred embodiment, the OSNA encodes a polypeptide having an amino acid sequence selected from SEQ ID NO: 249-396, or a homolog, allelic variant or fragment thereof. In a more preferred embodiment, the OSNA has a nucleotide sequence selected from SEQ ID NO: 1-248, or a hybridizing nucleic acid, an allelic variant or a part thereof. Determining whether a sample expresses a OSNA can be accomplished by any method known in the art. Preferred methods include hybridization to microarrays, Northern blot hybridization, and quantitative or qualitative RT-PCR. In another preferred embodiment, the method can be practiced by determining whether a OSP is expressed. Determining whether a sample expresses a OSP can be accomplished by any method known in the art. Preferred methods include Western blot, ELISA, RIA and 2D PAGE. In one embodiment, the OSP has an amino acid sequence selected from SEQ ID NO: 249-396, or a homolog, allelic variant or fragment thereof. In

another preferred embodiment, the expression of at least two OSNAs and/or OSPs is determined. In a more preferred embodiment, the expression of at least three, more preferably four and even more preferably five OSNAs and/or OSPs are determined.

In one embodiment, the method can be used to determine whether an unknown tissue is ovarian tissue. This is particularly useful in forensic science, in which small, damaged pieces of tissues that are not identifiable by microscopic or other means are recovered from a crime or accident scene. In another embodiment, the method can be used to determine whether a tissue is differentiating or developing into ovarian tissue. This is important in monitoring the effects of the addition of various agents to cell or tissue culture, *e.g.*, in producing new ovarian tissue by tissue engineering. These agents include, *e.g.*, growth and differentiation factors, extracellular matrix proteins and culture medium. Other factors that may be measured for effects on tissue development and differentiation include gene transfer into the cells or tissues, alterations in pH, aqueous:air interface and various other culture conditions.

Methods for Producing and Modifying ovarian Tissue

In another aspect, the invention provides methods for producing engineered ovarian tissue or cells. In one embodiment, the method comprises the steps of providing cells, introducing a OSNA or a OSG into the cells, and growing the cells under conditions in which they exhibit one or more properties of ovarian tissue cells. In a preferred embodiment, the cells are pleuripotent. As is well known in the art, normal ovarian tissue comprises a large number of different cell types. Thus, in one embodiment, the engineered ovarian tissue or cells comprises one of these cell types. In another embodiment, the engineered ovarian tissue or cells comprises more than one ovarian cell type. Further, the culture conditions of the cells or tissue may require manipulation in order to achieve full differentiation and development of the ovarian cell tissue. Methods for manipulating culture conditions are well known in the art.

Nucleic acid molecules encoding one or more OSPs are introduced into cells, preferably pleuripotent cells. In a preferred embodiment, the nucleic acid molecules encode OSPs having amino acid sequences selected from SEQ ID NO: 249-396, or homologous proteins, analogs, allelic variants or fragments thereof. In a more preferred embodiment, the nucleic acid molecules have a nucleotide sequence selected from SEQ ID NO: 1-248, or hybridizing nucleic acids, allelic variants or parts thereof. In another highly

preferred embodiment, a OSG is introduced into the cells. Expression vectors and methods of introducing nucleic acid molecules into cells are well known in the art and are described in detail, *supra*.

Artificial ovarian tissue may be used to treat patients who have lost some or all of their ovarian function.

Pharmaceutical Compositions

In another aspect, the invention provides pharmaceutical compositions comprising the nucleic acid molecules, polypeptides, fusion proteins, antibodies, antibody derivatives, antibody fragments, agonists, antagonists, or inhibitors of the present invention. In a preferred embodiment, the pharmaceutical composition comprises a OSNA or part thereof. In a more preferred embodiment, the OSNA has a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-248, a nucleic acid that hybridizes thereto, an allelic variant thereof, or a nucleic acid that has substantial sequence identity thereto. In another preferred embodiment, the pharmaceutical composition comprises a OSP or fragment thereof. In a more preferred embodiment, the pharmaceutical composition comprises a OSP having an amino acid sequence that is selected from the group consisting of SEQ ID NO: 249-396, a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof. In another preferred embodiment, the pharmaceutical composition comprises an anti-OSP antibody, preferably an antibody that specifically binds to a OSP having an amino acid that is selected from the group consisting of SEQ ID NO: 249-396, or an antibody that binds to a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof.

Such a composition typically contains from about 0.1 to 90% by weight of a therapeutic agent of the invention formulated in and/or with a pharmaceutically acceptable carrier or excipient.

Pharmaceutical formulation is a well-established art that is further described in Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th ed., Lippincott, Williams & Wilkins (2000); Ansel *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippincott Williams & Wilkins (1999); and Kibbe (ed.), Handbook of Pharmaceutical Excipients American Pharmaceutical Association, 3rd ed. (2000) and thus need not be described in detail herein.

Briefly, formulation of the pharmaceutical compositions of the present invention will depend upon the route chosen for administration. The pharmaceutical compositions utilized in this invention can be administered by various routes including both enteral and parenteral routes, including oral, intravenous, intramuscular, subcutaneous, inhalation, topical, sublingual, rectal, intra-arterial, intramedullary, intrathecal, intraventricular, transmucosal, transdermal, intranasal, intraperitoneal, intrapulmonary, and intrauterine.

Oral dosage forms can be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Solid formulations of the compositions for oral administration can contain suitable carriers or excipients, such as carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or microcrystalline cellulose; gums including arabic and tragacanth; proteins such as gelatin and collagen; inorganics, such as kaolin, calcium carbonate, dicalcium phosphate, sodium chloride; and other agents such as acacia and alginic acid.

Agents that facilitate disintegration and/or solubilization can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate, microcrystalline cellulose, cornstarch, sodium starch glycolate, and alginic acid.

Tablet binders that can be used include acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone™), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

Lubricants that can be used include magnesium stearates, stearic acid, silicone fluid, talc, waxes, oils, and colloidal silica.

Fillers, agents that facilitate disintegration and/or solubilization, tablet binders and lubricants, including the aforementioned, can be used singly or in combination.

Solid oral dosage forms need not be uniform throughout. For example, dragee cores can be used in conjunction with suitable coatings, such as concentrated sugar solutions, which can also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

Oral dosage forms of the present invention include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or

sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Additionally, dyestuffs or pigments can be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, *i.e.*, dosage.

Liquid formulations of the pharmaceutical compositions for oral (enteral) administration are prepared in water or other aqueous vehicles and can contain various suspending agents such as methylcellulose, alginates, tragacanth, pectin, kelgin, carrageenan, acacia, polyvinylpyrrolidone, and polyvinyl alcohol. The liquid formulations can also include solutions, emulsions, syrups and elixirs containing, together with the active compound(s), wetting agents, sweeteners, and coloring and flavoring agents.

The pharmaceutical compositions of the present invention can also be formulated for parenteral administration. Formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions.

For intravenous injection, water soluble versions of the compounds of the present invention are formulated in, or if provided as a lyophilate, mixed with, a physiologically acceptable fluid vehicle, such as 5% dextrose ("D5"), physiologically buffered saline, 0.9% saline, Hanks' solution, or Ringer's solution. Intravenous formulations may include carriers, excipients or stabilizers including, without limitation, calcium, human serum albumin, citrate, acetate, calcium chloride, carbonate, and other salts.

Intramuscular preparations, *e.g.* a sterile formulation of a suitable soluble salt form of the compounds of the present invention, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution. Alternatively, a suitable insoluble form of the compound can be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, such as an ester of a long chain fatty acid (*e.g.*, ethyl oleate), fatty oils such as sesame oil, triglycerides, or liposomes.

Parenteral formulations of the compositions can contain various carriers such as vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like).

Aqueous injection suspensions can also contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Non-lipid polycationic amino polymers can also be used for delivery. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical compositions of the present invention can also be formulated to permit injectable, long-term, deposition. Injectable depot forms may be made by forming microencapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in microemulsions that are compatible with body tissues.

The pharmaceutical compositions of the present invention can be administered topically. For topical use the compounds of the present invention can also be prepared in suitable forms to be applied to the skin, or mucus membranes of the nose and throat, and can take the form of lotions, creams, ointments, liquid sprays or inhalants, drops, tinctures, lozenges, or throat paints. Such topical formulations further can include chemical compounds such as dimethylsulfoxide (DMSO) to facilitate surface penetration of the active ingredient. In other transdermal formulations, typically in patch-delivered formulations, the pharmaceutically active compound is formulated with one or more skin penetrants, such as 2-N-methyl-pyrrolidone (NMP) or Azone. A topical semi-solid ointment formulation typically contains a concentration of the active ingredient from about 1 to 20%, *e.g.*, 5 to 10%, in a carrier such as a pharmaceutical cream base.

For application to the eyes or ears, the compounds of the present invention can be presented in liquid or semi-liquid form formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints or powders.

For rectal administration the compounds of the present invention can be administered in the form of suppositories admixed with conventional carriers such as cocoa butter, wax or other glyceride.

Inhalation formulations can also readily be formulated. For inhalation, various powder and liquid formulations can be prepared. For aerosol preparations, a sterile formulation of the compound or salt form of the compound may be used in inhalers, such

as metered dose inhalers, and nebulizers. Aerosolized forms may be especially useful for treating respiratory disorders.

Alternatively, the compounds of the present invention can be in powder form for reconstitution in the appropriate pharmaceutically acceptable carrier at the time of delivery.

The pharmaceutically active compound in the pharmaceutical compositions of the present invention can be provided as the salt of a variety of acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

After pharmaceutical compositions have been prepared, they are packaged in an appropriate container and labeled for treatment of an indicated condition.

The active compound will be present in an amount effective to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

A "therapeutically effective dose" refers to that amount of active ingredient, for example OSP polypeptide, fusion protein, or fragments thereof, antibodies specific for OSP, agonists, antagonists or inhibitors of OSP, which ameliorates the signs or symptoms of the disease or prevent progression thereof; as would be understood in the medical arts, cure, although desired, is not required.

The therapeutically effective dose of the pharmaceutical agents of the present invention can be estimated initially by *in vitro* tests, such as cell culture assays, followed by assay in model animals, usually mice, rats, rabbits, dogs, or pigs. The animal model can also be used to determine an initial preferred concentration range and route of administration.

For example, the ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population) can be determined in one or more cell culture of animal model systems. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as LD50/ED50. Pharmaceutical compositions that exhibit large therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies are used in formulating an initial dosage range for human use, and preferably provide a range of circulating concentrations that includes the ED50 with little or no toxicity. After

administration, or between successive administrations, the circulating concentration of active agent varies within this range depending upon pharmacokinetic factors well known in the art, such as the dosage form employed, sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors specific to the subject requiring treatment. Factors that can be taken into account by the practitioner include the severity of the disease state, general health of the subject, age, weight, gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration. Where the therapeutic agent is a protein or antibody of the present invention, the therapeutic protein or antibody agent typically is administered at a daily dosage of 0.01 mg to 30 mg/kg of body weight of the patient (*e.g.*, 1mg/kg to 5 mg/kg). The pharmaceutical formulation can be administered in multiple doses per day, if desired, to achieve the total desired daily dose.

Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical formulation(s) of the present invention to the patient. The pharmaceutical compositions of the present invention can be administered alone, or in combination with other therapeutic agents or interventions.

Therapeutic Methods

The present invention further provides methods of treating subjects having defects in a gene of the invention, *e.g.*, in expression, activity, distribution, localization, and/or solubility, which can manifest as a disorder of ovarian function. As used herein, "treating" includes all medically-acceptable types of therapeutic intervention, including palliation and prophylaxis (prevention) of disease. The term "treating" encompasses any

improvement of a disease, including minor improvements. These methods are discussed below.

Gene Therapy and Vaccines

The isolated nucleic acids of the present invention can also be used to drive *in vivo* expression of the polypeptides of the present invention. *In vivo* expression can be driven from a vector, typically a viral vector, often a vector based upon a replication incompetent retrovirus, an adenovirus, or an adeno-associated virus (AAV), for the purpose of gene therapy. *In vivo* expression can also be driven from signals endogenous to the nucleic acid or from a vector, often a plasmid vector, such as pVAX1 (Invitrogen, Carlsbad, CA, USA), for purpose of "naked" nucleic acid vaccination, as further described in U.S. Patent Nos. 5,589,466; 5,679,647; 5,804,566; 5,830,877; 5,843,913; 5,880,104; 5,958,891; 5,985,847; 6,017,897; 6,110,898; 6,204,250, the disclosures of which are incorporated herein by reference in their entireties. For cancer therapy, it is preferred that the vector also be tumor-selective. *See, e.g.*, Doronin *et al.*, *J. Virol.* 75: 3314-24 (2001).

In another embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a nucleic acid molecule of the present invention is administered. The nucleic acid molecule can be delivered in a vector that drives expression of a OSP, fusion protein, or fragment thereof, or without such vector. Nucleic acid compositions that can drive expression of a OSP are administered, for example, to complement a deficiency in the native OSP, or as DNA vaccines. Expression vectors derived from virus, replication deficient retroviruses, adenovirus, adeno-associated (AAV) virus, herpes virus, or vaccinia virus can be used as can plasmids. *See, e.g.*, Cid-Arregui, *supra*. In a preferred embodiment, the nucleic acid molecule encodes a OSP having the amino acid sequence of SEQ ID NO: 249-396, or a fragment, fusion protein, allelic variant or homolog thereof.

In still other therapeutic methods of the present invention, pharmaceutical compositions comprising host cells that express a OSP, fusions, or fragments thereof can be administered. In such cases, the cells are typically autologous, so as to circumvent xenogeneic or allotypic rejection, and are administered to complement defects in OSP production or activity. In a preferred embodiment, the nucleic acid molecules in the cells encode a OSP having the amino acid sequence of SEQ ID NO: 249-396, or a fragment, fusion protein, allelic variant or homolog thereof.

Antisense Administration

Antisense nucleic acid compositions, or vectors that drive expression of a OSG antisense nucleic acid, are administered to downregulate transcription and/or translation of a OSG in circumstances in which excessive production, or production of aberrant protein, is the pathophysiologic basis of disease.

Antisense compositions useful in therapy can have a sequence that is complementary to coding or to noncoding regions of a OSG. For example, oligonucleotides derived from the transcription initiation site, *e.g.*, between positions -10 and +10 from the start site, are preferred.

Catalytic antisense compositions, such as ribozymes, that are capable of sequence-specific hybridization to OSG transcripts, are also useful in therapy. *See, e.g.*, Phylactou, *Adv. Drug Deliv. Rev.* 44(2-3): 97-108 (2000); Phylactou *et al.*, *Hum. Mol. Genet.* 7(10): 1649-53 (1998); Rossi, *Ciba Found. Symp.* 209: 195-204 (1997); and Sigurdsson *et al.*, *Trends Biotechnol.* 13(8): 286-9 (1995).

Other nucleic acids useful in the therapeutic methods of the present invention are those that are capable of triplex helix formation in or near the OSG genomic locus. Such triplexing oligonucleotides are able to inhibit transcription. *See, e.g.,* Intody *et al.*, *Nucleic Acids Res.* 28(21): 4283-90 (2000); and McGuffie *et al.*, *Cancer Res.* 60(14): 3790-9 (2000). Pharmaceutical compositions comprising such triplex forming oligos (TFOs) are administered in circumstances in which excessive production, or production of aberrant protein, is a pathophysiologic basis of disease.

In a preferred embodiment, the antisense molecule is derived from a nucleic acid molecule encoding a OSP, preferably a OSP comprising an amino acid sequence of SEQ ID NO: 249-396, or a fragment, allelic variant or homolog thereof. In a more preferred embodiment, the antisense molecule is derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-248, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

Polypeptide Administration

In one embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a OSP, a fusion protein, fragment, analog or derivative thereof is administered to a subject with a clinically-significant OSP defect.

Protein compositions are administered, for example, to complement a deficiency in native OSP. In other embodiments, protein compositions are administered as a vaccine to elicit a humoral and/or cellular immune response to OSP. The immune response can be used to modulate activity of OSP or, depending on the immunogen, to immunize against aberrant or aberrantly expressed forms, such as mutant or inappropriately expressed isoforms. In yet other embodiments, protein fusions having a toxic moiety are administered to ablate cells that aberrantly accumulate OSP.

In a preferred embodiment, the polypeptide administered is a OSP comprising an amino acid sequence of SEQ ID NO: 249-396, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the polypeptide is encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-248, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

Antibody, Agonist and Antagonist Administration

In another embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising an antibody (including fragment or derivative thereof) of the present invention is administered. As is well known, antibody compositions are administered, for example, to antagonize activity of OSP, or to target therapeutic agents to sites of OSP presence and/or accumulation. In a preferred embodiment, the antibody specifically binds to a OSP comprising an amino acid sequence of SEQ ID NO: 249-396, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the antibody specifically binds to a OSP encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-248, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

The present invention also provides methods for identifying modulators which bind to a OSP or have a modulatory effect on the expression or activity of a OSP. Modulators which decrease the expression or activity of OSP (antagonists) are believed to be useful in treating ovarian cancer. Such screening assays are known to those of skill in the art and include, without limitation, cell-based assays and cell-free assays. Small molecules predicted via computer imaging to specifically bind to regions of a OSP can also be designed, synthesized and tested for use in the imaging and treatment of ovarian cancer. Further, libraries of molecules can be screened for potential anticancer agents by assessing the ability of the molecule to bind to the OSPs identified herein. Molecules

identified in the library as being capable of binding to a OSP are key candidates for further evaluation for use in the treatment of ovarian cancer. In a preferred embodiment, these molecules will downregulate expression and/or activity of a OSP in cells.

In another embodiment of the therapeutic methods of the present invention, a pharmaceutical composition comprising a non-antibody antagonist of OSP is administered. Antagonists of OSP can be produced using methods generally known in the art. In particular, purified OSP can be used to screen libraries of pharmaceutical agents, often combinatorial libraries of small molecules, to identify those that specifically bind and antagonize at least one activity of a OSP.

In other embodiments a pharmaceutical composition comprising an agonist of a OSP is administered. Agonists can be identified using methods analogous to those used to identify antagonists.

In a preferred embodiment, the antagonist or agonist specifically binds to and antagonizes or agonizes, respectively, a OSP comprising an amino acid sequence of SEQ ID NO: 249-396, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the antagonist or agonist specifically binds to and antagonizes or agonizes, respectively, a OSP encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-248, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

Targeting ovarian Tissue

The invention also provides a method in which a polypeptide of the invention, or an antibody thereto, is linked to a therapeutic agent such that it can be delivered to the ovarian or to specific cells in the ovarian. In a preferred embodiment, an anti-OSP antibody is linked to a therapeutic agent and is administered to a patient in need of such therapeutic agent. The therapeutic agent may be a toxin, if ovarian tissue needs to be selectively destroyed. This would be useful for targeting and killing ovarian cancer cells. In another embodiment, the therapeutic agent may be a growth or differentiation factor, which would be useful for promoting ovarian cell function.

In another embodiment, an anti-OSP antibody may be linked to an imaging agent that can be detected using, *e.g.*, magnetic resonance imaging, CT or PET. This would be useful for determining and monitoring ovarian function, identifying ovarian cancer tumors, and identifying noncancerous ovarian diseases.

EXAMPLES

Example 1a: Gene Expression Analysis

Identification of OSGs was carried out by a systematic analysis of gene expression data in the LIFESEQ® Gold database available from Incyte Genomics Inc, Palo Alto, CA, using the data mining software package CLASP™.

The CLASP target gene identification process is focused on, but not limited to, the following 5 CLASP profiles: tissue specific expression, cancer specific expression, differentially expressed in cancer, maximum tissue differential expression.

1. For these profiles: cDNA libraries were divided into 60 unique tissue organs. The genes were grouped into gene bins, each bin is a sequence based cluster grouped together with a common contig. The expression levels for each gene bin were calculated in each organ. Differential expression significance was calculated with rigorous statistical significant test considering the influence of sequence random fluctuations and sampling size of cDNA libraries from concept published by Audic S and Claverie JM (Genome Res 1997 7(10): 986-995: The significance of digital gene expression profiles).
2. Highly expressed organ specific genes were selected based on the percentage abundance level in the targeted organ versus all the other organs (organ-specificity).
3. The expression levels of each highly expressed organ-specific gene in the tumor tissue libraries were compared with normal tissue libraries and tissue libraries associated with tumor or disease (cancer-specificity) and analyzed for statistical significance.
4. Target genes exhibiting each CLASP profile criteria were selected.

CLASP 1 tissue specific expression profile: In order to meet the organ-specificity criteria, the expression level of the component clones which the gene is composed of must exhibit three or more occurrences regardless the total number of genes isolated for the target organ. The percentage abundance level in each organ was calculated to identify the organ with the highest expression percentage level.

CLASP 2 cancer specific expression profile: In order to fulfill the cancer specific criteria, genes must exhibit zero expression in normal libraries and measurable expression

in libraries associated with tumor and/or disease. The gene must also exhibit organ-specificity to be selected as a CLASP target for this profile.

CLASP 3 maximum tissue differential expression profile: CLASP targets were selected based on ratio of expression in tumor libraries compared to expression in normal libraries (including normal libraries associated with tumor or disease) for each organ regardless of whether the gene exhibited organ-specificity. This profile was divided into 2 sub-profiles, since the ratio of expression cannot be obtained if no expression is present in normal libraries (including normal libraries associated with tumor or disease). In this case, the maximum expression percentage of the gene was calculated by measuring the occurrence of the gene divided by the occurrence of all genes in the target organ. CLASP selects the top 50 targets for each sub-profile.

CLASP 4 maximum tissue differential expression profile with negligible expression in normal tissues: CLASP targets were selected based on ratio of expression in tumor libraries compared to expression in normal libraries (including normal libraries associated with tumor or disease) for each organ regardless of whether the gene exhibited organ-specificity.

CLASP 5 differentially expressed in cancer profile: Expression levels in tumor libraries in each organ and normal libraries (including normal libraries associated with cancer or disease) for all organs were obtained and statistically analyzed. If the gene exhibited 90% of confidence that it is over-expressed in tumor libraries in the target organ than normal libraries for all organs, it was selected as a CLASP target for this profile.

Accordingly, CLASP allows the identification of highly expressed organ and cancer specific genes based on the gene expression levels in each tissue organ. CLASP scores for a portion of the OSG of this invention are listed below.

DEX0337_X	CLASP
DEX0337_1	CLASP5 CLASP3
DEX0337_2	CLASP5 CLASP4
DEX0337_3	CLASP5 CLASP3
DEX0337_4	CLASP5 CLASP3
DEX0337_5	CLASP5
DEX0337_6	CLASP5
DEX0337_7	CLASP5
DEX0337_8	CLASP5
DEX0337_9	CLASP5
DEX0337_10	CLASP5
DEX0337_13	CLASP5
DEX0337_14	CLASP5

DEX0337_15	CLASP5
DEX0337_16	CLASP5
DEX0337_17	CLASP5
DEX0337_18	CLASP5
DEX0337_19	CLASP5
DEX0337_20	CLASP5
DEX0337_21	CLASP5
DEX0337_24	CLASP5
DEX0337_25	CLASP5
DEX0337_26	CLASP5 CLASP4 CLASP3
DEX0337_30	CLASP5
DEX0337_31	CLASP5
DEX0337_32	CLASP5 CLASP4
DEX0337_33	CLASP5
DEX0337_34	CLASP5 CLASP4
DEX0337_35	CLASP5 CLASP4
DEX0337_36	CLASP5 CLASP4
DEX0337_37	CLASP5 CLASP4
DEX0337_38	CLASP5 CLASP4
DEX0337_39	CLASP5 CLASP4
DEX0337_40	CLASP5
DEX0337_41	CLASP5
DEX0337_42	CLASP5 CLASP3
DEX0337_43	CLASP5
DEX0337_44	CLASP5
DEX0337_45	CLASP5 CLASP4
DEX0337_46	CLASP5 CLASP4
DEX0337_47	CLASP5 CLASP4
DEX0337_48	CLASP5 CLASP1 CLASP3 CLASP4
DEX0337_49	CLASP5 CLASP3 CLASP4
DEX0337_50	CLASP5 CLASP3 CLASP4
DEX0337_51	CLASP5
DEX0337_52	CLASP5
DEX0337_53	CLASP5
DEX0337_54	CLASP5
DEX0337_55	CLASP5
DEX0337_56	CLASP5
DEX0337_57	CLASP5
DEX0337_60	CLASP5
DEX0337_61	CLASP5
DEX0337_62	CLASP5
DEX0337_63	CLASP5
DEX0337_64	CLASP5
DEX0337_65	CLASP5 CLASP1 CLASP3 CLASP4
DEX0337_66	CLASP5
DEX0337_67	CLASP5
DEX0337_68	CLASP5
DEX0337_69	CLASP5 CLASP4
DEX0337_70	CLASP5
DEX0337_71	CLASP5
DEX0337_72	CLASP5 CLASP3
DEX0337_73	CLASP5 CLASP3
DEX0337_74	CLASP5 CLASP4
DEX0337_102	CLASP2
DEX0337_103	CLASP2
DEX0337_104	CLASP2
DEX0337_105	CLASP2

In addition the expression values for each organ in the format 9 - 0.9999 are listed. Each column first lists the given organ (ORG), a number representing the percentage of the expression (EXP) of the gene in the given organ.

DEX0337_X	Org Exp	Org Exp	Org Exp	Org Exp	Org Exp
DEX0337_1	OVR .2677	PIB .0363	FAL .0503	BMR .0515	SPC .06
DEX0337_2	OVR .2339	MSL .0845	SAG .0988	BNC .1085	UNC .1236
DEX0337_3	OVR .0021	BRN .0013	UTR .0013	BLD .0016	BLV .0016
DEX0337_4	OVR .0021	BRN .0013	UTR .0013	BLD .0016	BLV .0016
DEX0337_5	OVR .001				
DEX0337_6	OVR .001				
DEX0337_7	OVR .001	BRN .0002			
DEX0337_8	OVR .001	CON .0011			
DEX0337_9	OVR .001				
DEX0337_10	OVR .001				
DEX0337_13	OVR .001				
DEX0337_14	OVR .001				
DEX0337_15	OVR .001				
DEX0337_16	OVR .001				
DEX0337_17	OVR .001				
DEX0337_18	OVR .001				
DEX0337_19	OVR .001				
DEX0337_20	OVR .001				
DEX0337_21	OVR .001				
DEX0337_24	OVR .0021	BRN .0002			
DEX0337_25	OVR .0021	BRN .0002			
DEX0337_26	ESO .0051	LIV .0076	LMN .0083	FAL .0189	
DEX0337_27	ESO .0051	LIV .0076	LMN .0083	FAL .0189	
DEX0337_28	OVR .0033	BRN .0001	PRO .0003	MAM .0004	UTR .0004
DEX0337_29	OVR .0492	BRN .0002	BRN .0002	CON .0034	CON .0034
DEX0337_30	OVR .001				
DEX0337_31	OVR .001				
DEX0337_32	OVR .0092	BLD .0016	BLV .0016	LIV .0019	FTS .002
DEX0337_33	THY .006	UTR .0069	KID .0128	PRO .0135	
DEX0337_34	OVR .0133	MSL .0053	SYN .0056	NOS .0073	UNC .008
DEX0337_35	OVR .8811	SAG .316	NOS .4326	FAL .4399	PLE .4486
DEX0337_36	OVR .8811	SAG .316	NOS .4326	FAL .4399	PLE .4486
DEX0337_37	OVR .0564	INT .015	NOS .0293	BMR .0322	BLO .036
DEX0337_38	OVR .677	BMR .1609	SAG .1778	SPC .1899	NOS .198
DEX0337_39	OVR .0092	PNS .0023	LMN .0028	THY .004	PAN .0047
DEX0337_40	CON .0011				
DEX0337_41	OVR .0636	BRN .0082	LNG .0207	GLB .0231	BLD .0273
DEX0337_42	OVR .0144	BRN .0029	BLV .0033	BLO .004	THY .004
DEX0337_43	OVR .0092	UNC .004	BON .0112		
DEX0337_44	OVR .0072	FTS .0018	PRO .004	MAM .0043	INL .009
DEX0337_45	OVR .0133	MSL .0053	SYN .0056	NOS .0073	UNC .008
DEX0337_46	OVR .0103	BRN .0006	BLV .0016	INL .0019	CRD .0023
DEX0337_47	OVR .0103	BRN .0006	BLV .0016	INL .0019	CRD .0023
DEX0337_48	OVR .1908	SAG .0593	SAG .0593	SAG .0593	INT .0798
DEX0337_49	OVR .1651	SPC .02	SPC .02	PIT .0205	PIT .0205
DEX0337_50	OVR .1651	SPC .02	SPC .02	PIT .0205	PIT .0205
DEX0337_51	OVR .0072	LNG .0011	KID .0026	BON .0056	
DEX0337_52	BRN .0199				

DEX0337_53	OVR .0031				
DEX0337_54	OVR .0031				
DEX0337_55	THY .006	UTR .0069	KID .0128	PRO .0135	
DEX0337_56	OVR .0051	ADR .003	CON .0045	BRN .0052	TON .0299
DEX0337_57	OVR .0698	BRN .03	FTS .0374	MAM .0397	PAN .0447
DEX0337_60	OVR .0031				
DEX0337_61	OVR .001				
DEX0337_62	OVR .001				
DEX0337_63	OVR .0062	FTS .0035	INS .0048	ADR .0089	BON .0112
DEX0337_64	OVR .0174	FTS .0023	PAN .0035	ESO .0051	
DEX0337_65	OVR .0328	TNS .0016	PNS .0022	PNS .0023	PNS .0023
DEX0337_66	OVR .0062	CRD .0023	UNC .004	STO .0041	PRO .0073
DEX0337_67	OVR .0318	UTR .0307	CON .034		
DEX0337_68	OVR .0195	LMN .0167	INL .0186	NOS .022	ESO .0256
DEX0337_69	OVR .8811	SAG .316	NOS .4326	FAL .4399	PLE .4486
DEX0337_70	OVR .0328				
DEX0337_71	OVR .0154	PNS .0047			
DEX0337_72	OVR .0174	BLO .004	ESO .0051	CON .0057	ADR .006
DEX0337_73	OVR .0174	BLO .004	ESO .0051	CON .0057	ADR .006
DEX0337_74	OVR .0154	LNG .0017	MSL .0026	TST .0027	ADR .003
DEX0337_102	OVR .0046				
DEX0337_103	OVR .0046				
DEX0337_104	OVR .0046				
DEX0337_105	OVR .0046				

Abbreviation for tissues:
ADR Adrenal Glands; BLD Bladder; BLO Blood; BLV Blood Vessels; BMR Bone Marrow; BNC Bronchi; BON Bones; BRN Brain; CON Connective Tissue; CRD Heart; ESO Esophagus; FAL Fallopian Tubes; FTS Fetus; GLB Gallbladder; INL Intestine, Large; INS Intestine, Small; INT Intestine; KID Kidney; LIV Liver; LMN Lymphoid Tissue; LNG Lung; MAM Breast; MSL Muscles; NOS Nose; OVR Ovary; PAN Pancreas; PIB Pineal Body; PIT Pituitary Gland; PLE Pleura; PNS Penis; PRO Prostate; SAG Salivary Glands; SPC Spinal Cord; STO Stomach; SYN Synovial Membranes; THY Thymus Gland; TNS Tonsil/Adenoids; TON Tongue; TST Testis; UNC Mixed Tissues; UTR Uterus

Example 1b: Suppression Subtractive Hybridization (Clontech PCR-SELECT)

Clontech PCR-SELECT is a PCR based subtractive hybridization method designed to selectively enrich for cDNAs corresponding to mRNAs differentially expressed between two mRNA populations (Diatchenko et al, Proc. Natl. Acad. Sci. USA, Vol. 93, pp. 6025-6030, 1996). Clontech PCR-SELECT is a method for enrichment of differentially expressed mRNAs based on a selective amplification. cDNA is prepared from the two mRNA populations which are to be compared (Tester: cDNA population in which the differentially expressed messages are sought and Driver: cDNA population in which the differentially expressed transcripts are absent or low). The tester sample is separated in two parts and different PCR adapters are ligated to the 5' ends. Each tester is separately annealed to excess driver (first annealing) and then pooled and again annealed (second annealing) to excess driver. During the first annealing sequences common to both populations anneal. Additionally the concentration of high and low abundance messages

are normalized since annealing is faster for abundant molecules due to the second order kinetics of hybridization. During the second annealing cDNAs unique or overabundant to the tester can anneal together. Such molecules have different adapters at their ends. The addition of additional driver during the second annealing enhances the enrichment of the desired differentially expressed sequences. During subsequent PCR, molecules that have different adapters at each end amplify exponentially. Molecules which have identical adapters, or adapters at only one end, or no adapters (driver sequences) either do not amplify or undergo linear amplification. The end result is enrichment for cDNAs corresponding to differentially expressed messages (unique to the tester or upregulated in the tester). This technique was used to identify transcripts unique to ovarian tissue or messages overexpressed in ovarian cancer. Pairs of matched samples isolated from the same patient, a cancer sample, and the "normal" adjacent tissue from the same tissue type were utilized. The mRNA from the cancer tissue is used as the "tester", and the non-cancer mRNA as a "driver". The non-cancer "driver" is from the same individual and tissue as the cancer sample (Matched). Alternatively, the "driver" can be from a different individual but the same tissue as the tumor sample (unmatched). In some cases mixtures of mRNAs derived from non-cancer tissues types different from the cancer tissue type are also used as "drivers". The last approach allows the identification of transcripts whose expression is specific or upregulated in the cancer tissue type analyzed. Such transcripts may or may not be cancer specific in their expression.

Several subtracted libraries were generated for ovarian tissue. The product of the subtraction experiments was used to generate cDNA libraries. These cDNA libraries contain Expressed Sequence Tags (ESTs) from genes that are ovarian cancer specific, or upregulated in ovarian tissue. Randomized clones picked from each cDNA PCR Select library were sequenced and the genes identified by a systematic analysis of the sequence data against the LIFESEQ Gold database available from Incyte Pharmaceuticals, Palo Alto.

Descriptions of the sequences from subtractions are as follows:

DEX0337_X
DEX0337_75
DEX0337_76
DEX0337_77
DEX0337_78
DEX0337_79
DEX0337_80
DEX0337_81

DEX0337_82
DEX0337_83
DEX0337_84
DEX0337_85
DEX0337_86
DEX0337_87
DEX0337_88
DEX0337_89
DEX0337_90
DEX0337_91
DEX0337_92
DEX0337_93
DEX0337_94
DEX0337_95
DEX0337_96
DEX0337_97
DEX0337_98
DEX0337_99
DEX0337_100
DEX0337_101

The sequence identifications and predicted peptide sequences for each of the targets are listed below:

DEX0337_X	ID	Predicted Peptide
DEX0337_1	mry2111	
DEX0337_2	mry3521	DEX0337_106
DEX0337_3	mry4157	DEX0337_107
DEX0337_4	flex mry4157	DEX0337_108
DEX0337_5	mry15155	DEX0337_109
DEX0337_6	flex mry15155	
DEX0337_7	mry15229	DEX0337_110
DEX0337_8	mry15272	
DEX0337_9	mry15337	DEX0337_111
DEX0337_10	flex mry15337	
DEX0337_11	mry15382	DEX0337_112
DEX0337_12	flex mry15382	
DEX0337_13	mry15405	DEX0337_113
DEX0337_14	flex mry15405	
DEX0337_15	mry15451	
DEX0337_16	mry15467	
DEX0337_17	mry15525	
DEX0337_18	mry15565	
DEX0337_19	mry15600	
DEX0337_20	mry15613	
DEX0337_21	mry15622	
DEX0337_22	mry15630	
DEX0337_23	flex mry15630	
DEX0337_24	mry15658	DEX0337_114
DEX0337_25	flex mry15658	
DEX0337_26	mry15673	
DEX0337_27	flex mry15673	
DEX0337_28	mry15778	
DEX0337_29	mry15781	
DEX0337_30	mry15859	DEX0337_115
DEX0337_31	flex mry15859	
DEX0337_32	mry15867	DEX0337_116

DEX0337_33	mry15874	DEX0337_117
DEX0337_34	mry15985	DEX0337_118
DEX0337_35	mry15996	DEX0337_119
DEX0337_36	mry15998	DEX0337_120
DEX0337_37	mry16007	DEX0337_121
DEX0337_38	mry16160	DEX0337_122
DEX0337_39	mry16164	DEX0337_123
DEX0337_40	flex mry16164	DEX0337_124
DEX0337_41	mry16208	DEX0337_125
DEX0337_42	mry16281	DEX0337_126
DEX0337_43	mry16285	
DEX0337_44	mry16315	DEX0337_127
DEX0337_45	mry16528	
DEX0337_46	mry16562	DEX0337_128
DEX0337_47	flex mry16562	DEX0337_129
DEX0337_48	mry16608	DEX0337_130
DEX0337_49	mry16623	DEX0337_131
DEX0337_50	flex mry16623	
DEX0337_51	mry16637	
DEX0337_52	mry16662	
DEX0337_53	mry16664	DEX0337_132
DEX0337_54	flex mry16664	
DEX0337_55	mry16679	DEX0337_133
DEX0337_56	mry16737	DEX0337_134
DEX0337_57	mry16788	DEX0337_135
DEX0337_58	mry16796	DEX0337_136
DEX0337_59	flex mry16796	
DEX0337_60	mry16808	
DEX0337_61	mry16823	DEX0337_137
DEX0337_62	flex mry16823	
DEX0337_63	mry16840	
DEX0337_64	mry16866	DEX0337_138
DEX0337_65	mry16881	DEX0337_139
DEX0337_66	mry16899	DEX0337_140
DEX0337_67	mry16905	
DEX0337_68	mry16953	
DEX0337_69	mry16983	DEX0337_141
DEX0337_70	mry16999	DEX0337_142
DEX0337_71	mry17001	DEX0337_143
DEX0337_72	mry17002	DEX0337_144
DEX0337_73	flex mry17002	DEX0337_145
DEX0337_74	mry17010	
DEX0337_75	mry26089	
DEX0337_76	mry26204	
DEX0337_77	mry26237	
DEX0337_78	mry26278	
DEX0337_79	mry26393	
DEX0337_80	mry26505	
DEX0337_81	mry26515	
DEX0337_82	mry26743	
DEX0337_83	mry26768	
DEX0337_84	mry26994	
DEX0337_85	mry27242	
DEX0337_86	mry27281	
DEX0337_87	mry27330	
DEX0337_88	mry27363	
DEX0337_89	mry27399	

DEX0337_90	mry27436	
DEX0337_91	mry27438	
DEX0337_92	mry27510	
DEX0337_93	mry27564	
DEX0337_94	mry27609	
DEX0337_95	mry27635	
DEX0337_96	mry27636	
DEX0337_97	mry27664	
DEX0337_98	mry27774	
DEX0337_99	mry27818	
DEX0337_100	mry28002	
DEX0337_101	mry28011	
DEX0337_102	mry31791	
DEX0337_103	flex mry31791	
DEX0337_104	mry33414	
DEX0337_105	mry33868	

The source of the parent sequences are as follows:

DEX0337_X	Parent	Library
DEX0337_75	26089	PSovr003
DEX0337_75	26089	PSovr007
DEX0337_75	26089	PSovr008
DEX0337_75	26089	PSovr009
DEX0337_75	26089	PSovr011
DEX0337_76	26204	PSovr005
DEX0337_77	26237	PSovr003
DEX0337_78	26278	PSovr003
DEX0337_79	26393	PSovr005
DEX0337_80	26505	PSovr007
DEX0337_81	26515	PSovr007
DEX0337_82	26743	PSovr008
DEX0337_83	26768	PSovr008
DEX0337_84	26994	PSovr009
DEX0337_85	27242	PSovr010
DEX0337_86	27281	PSovr010
DEX0337_87	27330	PSovr010
DEX0337_88	27363	PSovr011
DEX0337_89	27399	PSovr011
DEX0337_90	27436	PSovr011
DEX0337_91	27438	PSovr011
DEX0337_92	27510	PSovr011
DEX0337_93	27564	PSovr011
DEX0337_94	27609	PSovr011
DEX0337_95	27635	PSovr012
DEX0337_96	27636	PSovr012
DEX0337_97	27664	PSovr012
DEX0337_98	27774	PSovr012
DEX0337_99	27818	PSovr012
DEX0337_100	28002	PSovr012
DEX0337_101	28011	PSovr012

The summary of samples for ovarian PCR Select cDNA subtraction are as follows:

library ID	Tester-Tissue I.D.	Driver Tissue

library ID	Tester-Tissue I.D.	Driver Tissue
PSovr003	Three ovarian tumor samples	Six normal tissues: kidney, pancreas, spleen, small intestine, heart, colon. All samples from Clontech, except for colon. Colon tissue ID: 9703C126RA
	1071C papillary cystadenocarcinoma	
	10050 papillary serous and endometrioid carcinoma	
	10400 papillary serous adenocarcinoma	
PSovr005	7070-97 cancer matching sample Papillary serous carcinoma	7060-97 NAT
PSovr007	Three ovarian tumor samples (papillary serous carcinoma)	From Clontech: pool of five normal ovaries.
	1071C papillary cystadenocarcinoma	
	10050 papillary serous and endometrioid carcinoma	
	10400 papillary serous adenocarcinoma	
PS.OVR008	2370V Invasive papillary serous adenocarcinoma	S9822105 papillary serous carcinoma of low malignant potential (LMP)
PS.OVR009	S9822105 papillary serous carcinoma of low malignant potential (LMP)	2370V Invasive papillary serous adenocarcinoma
PS.OVR010	VNM00329 mucinous cystadenocarcinoma	14638A1C mucinous cystic neoplasm of Low Malignant Potential
PS.OVR011	14638A1C mucinous cystic neoplasm of Low Malignant Potential	VNM00329 mucinous cystadenocarcinoma
PS.OVR012	Pool of three	Other female cancers: breast, endometrium, cervix and uterus. breast: 9703B011d; uterus: 850U; endometrium: 9901A185; cervix: VNM0056001
	1071C papillary cystadenocarcinoma	
	10400 papillary serous adenocarcinoma	
	2370V Invasive papillary serous adenocarcinoma	

Example 2: Gene Expression Analysis

Custom Microarray Experiment—Ovarian Cancer

The source of the parent sequences for microarray were as follows: Parent sequences DEX0337_5 - DEX0337_27 were obtained from CLASP mining of the LifeSeq Gold sequence database. Parent sequences DEX0337_75 - DEX0337_101 were obtained by the subtraction experiments experiments previously described. Parent sequences DEX0337_1 - DEX0337_4 and DEX0337_28 - DEX0337_74 were obtained by sequence assembly using ESTs from both the subtractions assembled with sequences from Incyte's LifeSeq Gold database.

Custom oligonucleotide microarrays were provided by Agilent Technologies, Inc. (Palo Alto, CA). The microarrays were fabricated by Agilent using their technology for the in-situ synthesis of 60mer oligonucleotides (Hughes, et al. 2001, Nature Biotechnology 19:342-347). The 60mer microarray probes were designed by Agilent, from gene sequences provided by diaDexus, using Agilent proprietary algorithms. Whenever possible two differents 60mers were designed for each gene of interest.

All microarray experiments were two-color experiments and were preformed using Agilent-recommended protocols and reagents. Briefly, each microarray was hybridized with cRNAs synthesized from polyA+ RNA, isolated from cancer and normal tissues, labeled with fluorescent dyes Cyanine3 and Cyanine5 (NEN Life Science Products, Inc., Boston, MA) using a linear amplification method (Agilent). In each experiment the experimental sample was polyA+ RNA isolated from cancer tissue from a single individual and the reference sample was a pool of polyA+ RNA isolated from normal tissues of the same organ as the cancerous tissue (i.e. normal ovarian tissue in experiments with ovarian cancer samples). Tissue descriptions are listed in the following table. Hybridizations were carried out at 60oC, overnight using Agilent in-situ hybridization buffer. Following washing, arrays were scanned with a GenePix 4000B Microarray Scanner (Axon Instruments, Inc., Union City, CA). The resulting images were analyzed with GenePix Pro 3.0 Microarray Acquisition and Analysis Software (Axon). Two different chip designs were evaluated with overlapping sets of a total of 19 samples, comparing the expression patterns of ovarian cancer derived polyA+ RNA to polyA+ RNA isolated from a pool of 9 normal ovarian tissues were analyzed. For Chip2 all 19 samples (14 invasive carcinomas (INV), 5 low malignant potential (LMP) samples) were analyzed and for Chip1 a subset of 17 of these samples (13 invasive carcinomas, 4 low malignant potential samples) were assessed.

Data normalization and expression profiling were done with Expressionist software from GeneData Inc. (Daly City, CA/Basel, Switzerland). Gene expression analysis was performed using only experiments that meet certain quality criteria. The quality criteria that experiments must meet are a combination of evaluations performed by the Expressionist software and evaluations performed manually using raw and normalized data. To evaluate raw data quality, detection limits (the mean signal for a replicated negative control + 2 Standard Deviations (SD)) for each channel were calculated. The detection limit is a measure of non-specific hybridization. Arrays with poor detection

limits were not analyzed and the experiments were repeated. To evaluate normalized data quality, positive control elements included in the array were utilized. These array features should have a mean ratio of 1 (no differential expression). If these features have a mean ratio of greater than 1.5-fold up or down, the experiments were not analyzed further and were repeated. In addition to traditional scatter plots demonstrating the distribution of signal in each experiment, the Expressionist software also has minimum thresholding criteria that employ user defined parameters to identify quality data. Only those features that meet the threshhold criteria were included in the filtering and analyses carried out by Expressionist. The thresholding settings employed require a minimum area percentage of 60% [(% pixels > background + 2SD)-(% pixels saturated)], and a minimum signal to noise ratio of 2.0 in both channels. By these criteria, very low expressors and saturated features were not included in analysis.

Relative expression data was collected from Expressionist based on filtering and clustering analyses. Up- and down- regulated genes were identified using criteria for percentage of valid values obtained, and the percentage of experiments in which the gene is up- or down-regulated. These criteria were set independently for each data set, depending on the size and the nature of the data set. The results for the statistically significant upregulated and downregulated genes are shown in Table 1 and Table2. The first three columns of each table contain information about the sequence itself (Oligo ID, Parent ID, and Patent#), the next 3 columns show the results obtained. '%valid' indicates the percentage of unique experiments total (n=17 for Chip1, n=19 for Chip2) in which a valid expression value was obtained, '%up' indicates the percentage of experiments in which up-regulation of at least 2-fold was observed, and '%down' indicates the percentage of the experiments in which down-regulation of at least 2-fold was observed. The last column in each table describes the location of the microarray probe (oligo) relative to the parent sequence. For genes that the parent sequence was extended using databases of public and proprietary sequences, the both the parent DEX number and the extended (FLEXS) DEX number are listed in the DEX ID column. In these cases, the site of the 60mer probe is listed in the last column.

Table 1. Sensitivity data for up-regulated genes.

DEX ID	Parent ID	OligoID	"%valid, n=17 *n=19"	"%up, n=17, *n=19"	"%up INV, n=13, *n=14"	"%up LMP, n=4, *n=5"	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0337_3 DEX0337_4	4157	5236	100*	31.6*	42.9*	0*	930	989	929	988

DEX ID	Parent ID	OligoID	"%valid, n=17 *n=19"	"%up , n=17, *n=19"	"%up INV, n=13, *n=14"	"%up LMP, n=4, *n=5"	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0337_5 DEX0337_6	15155	26294.01	100	41.2	46.2	25	1056	1115	1049	1108
DEX0337_5 DEX0337_6	15155	26294.02	94.1	35.3	38.5	25	1056	1115	1049	1108
DEX0337_8	15272	32650.01	94.1	41.2	46.2	25	406	465		
DEX0337_8	15272	32650.02	94.1	47.1	53.8	25	406	465		
DEX0337_13 DEX0337_14	15405	13911.01	100	23.5	30.8	0	203	262	70	11
DEX0337_13 DEX0337_14	15405	13911.02	88.2	29.4	30.8	25	203	262	70	11
DEX0337_16	15467	15613.01	100	35.3	46.2	0	516	575		
DEX0337_16	15467	15613.02	94.1	41.2	53.8	0	516	575		
DEX0337_22 DEX0337_23	15630	17604.01	52.9	23.5	30.8	0	885	944	947	1006
DEX0337_22 DEX0337_23	15630	17604.02	41.2	35.3	38.5	25	885	944	947	1006
DEX0337_24 DEX0337_25	15658	10312.01	88.2	29.4	38.5	0	505	564	637	696
DEX0337_24 DEX0337_25	15658	10312.02	88.2	29.4	30.8	25	505	564	637	696
DEX0337_26 DEX0337_27	15673	26480.01	88.2	0	0	0	430	489	630	689
DEX0337_26 DEX0337_27	15673	26480.02	82.4	23.5	30.8	0	430	489	630	689
DEX0337_29	15781	14712.01	64.7	41.2	30.8	75	91	150		
DEX0337_29	15781	14712.02	70.6	47.1	30.8	100	91	150		
DEX0337_32	15867	16318.01	100	23.5	30.8	0	172	231		
DEX0337_32	15867	16318.02	100	23.5	30.8	0	172	231		
DEX0337_33	15874	16374.01	100	23.5	30.8	0	1793	1852		
DEX0337_33	15874	16374.02	100	17.6	23.1	0	1793	1852		
DEX0337_34	15985	17430.01	100	23.5	30.8	0	833	892		
DEX0337_34	15985	17430.02	100	17.6	23.1	0	833	892		
DEX0337_35	15996	17482.01	100	35.3	30.8	50	179	238		
DEX0337_35	15996	17482.02	100	41.2	38.5	50	179	238		
DEX0337_36	15998	17490.01	100	52.9	53.8	50	469	528		
DEX0337_36	15998	17490.02	100	58.8	53.8	75	469	528		
DEX0337_37	16007	18044.01	100	58.8	76.9	0	220	279		
DEX0337_37	16007	18044.02	100	64.7	84.6	0	220	279		
DEX0337_42	16281	20773.01	100	17.6	23.1	0	2181	2240		
DEX0337_42	16281	20773.02	94.1	23.5	30.8	0	2181	2240		
DEX0337_43	16285	20785.01	70.6	17.6	7.7	50	347	406		
DEX0337_43	16285	20785.02	82.4	17.6	7.7	50	347	406		
DEX0337_44	16315	21433.01	100	64.7	61.5	75	1550	1609		
DEX0337_44	16315	21433.02	100	64.7	61.5	75	1550	1609		
DEX0337_45	16528	23466.01	88.2	17.6	23.1	0	1621	1680		
DEX0337_45	16528	23466.02	100	23.5	30.8	0	1621	1680		
DEX0337_46 DEX0337_47	16562	23690.01	100	23.5	23.1	25	495	554	496	555
DEX0337_46 DEX0337_47	16562	23690.02	100	29.4	30.8	25	495	554	496	555
DEX0337_48	16608	24524.01	100	70.6	69.2	75	967	1026		
DEX0337_48	16608	24524.02	100	70.6	69.2	75	967	1026		
DEX0337_55	16679	25036.01	100	29.4	23.1	50	2243	2302		
DEX0337_55	16679	25036.02	100	29.4	23.1	50	2243	2302		
DEX0337_56	16737	9720.01	100	47.1	38.5	75	2070	2129		
DEX0337_56	16737	9720.02	100	52.9	46.2	75	2070	2129		
DEX0337_58 DEX0337_59	16796	9958.01	100	47.1	46.2	50	1339	1398	193	134
DEX0337_58 DEX0337_59	16796	9958.02	100	47.1	46.2	50	1339	1398	193	134
DEX0337_60	16808	10394.01	76.5	23.5	7.7	75	459	518		
DEX0337_60	16808	10394.02	82.4	23.5	7.7	75	459	518		
DEX0337_61 DEX0337_62	16823	10460.01	35.3	5.9	0	25	1800	1859	1801	1860
DEX0337_61 DEX0337_62	16823	10460.02	88.2	23.5	15.4	50	1800	1859	1801	1860
DEX0337_63	16840	10528.01	100	35.3	38.5	25	2731	2790		

DEX ID	Parent ID	OligoID	"%valid, n=17 *n=19"	"%up , n=17, *n=19"	"%up INV, n=13, *n=14"	"%up LMP, n=4, *n=5"	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0337_63	16840	10528.02	100	35.3	38.5	25	2731	2790		
DEX0337_64	16866	10636.01	94.1	23.5	7.7	75	2655	2714		
DEX0337_64	16866	10636.02	88.2	23.5	7.7	75	2655	2714		
DEX0337_65	16881	10702.01	100	94.1	92.3	100	2409	2468		
DEX0337_65	16881	10702.02	100	94.1	92.3	100	2409	2468		
DEX0337_66	16899	10764.01	100	29.4	30.8	25	3450	3509		
DEX0337_66	16899	10764.02	100	23.5	30.8	0	3450	3509		
DEX0337_69	16983	11575.01	100	52.9	53.8	50	1687	1746		
DEX0337_69	16983	11575.02	100	52.9	53.8	50	1687	1746		
DEX0337_74	17010#	12167.01	94.1	29.4	38.5	0	103	162		
DEX0337_74	17010#	12167.02	100	11.8	15.4	0	103	162		
DEX0337_75	26089	56828.01	100	64.7	69.2	50	543	602		
DEX0337_75	26089	56828.02	100	64.7	53.8	100	543	602		
DEX0337_77	26237	97624.01	70.6	35.3	38.5	25	32	91		
DEX0337_77	26237	97624.02	70.6	23.5	23.1	25	32	91		
DEX0337_82	26743#	58509.01	94.1	29.4	30.8	25	222	281		
DEX0337_82	26743#	58509.02	100	35.3	38.5	25	222	281		
DEX0337_84	26994	59208.01	100	17.6	15.4	25	990	1049		
DEX0337_84	26994	59208.02	100	17.6	7.7	50	990	1049		
DEX0337_85	27242	59985.01	100	35.3	46.2	0	557	616		
DEX0337_85	27242	59985.02	100	35.3	46.2	0	557	616		
DEX0337_89	27399	70536.01	100	11.8	7.7	25	370	429		
DEX0337_89	27399	70536.02	100	23.5	7.7	75	370	429		
DEX0337_92	27510	70956.01	100	23.5	7.7	75	836	895		
DEX0337_92	27510	70956.02	100	23.5	7.7	75	836	895		
DEX0337_95	27635	71412.01	100	17.6	7.7	50	935	994		
DEX0337_95	27635	71412.02	100	17.6	7.7	50	935	994		
DEX0337_96	27636#	71416.01	100	5.9	7.7	0	867	926		
DEX0337_96	27636#	71416.02	100	17.6	7.7	50	867	926		
DEX0337_98	27774	71900.01	70.6	41.2	46.2	25	466	525		
DEX0337_98	27774	71900.02	47.1	29.4	30.8	25	466	525		
DEX0337_99	27818#	72043.01	94.1	29.4	30.8	25	945	1004		
DEX0337_99	27818#	72043.02	82.4	11.8	7.7	25	945	1004		
DEX0337_102 DEX0337_103	31791	92877.01	52.9	23.5	30.8	0	445	504	443	502
DEX0337_102 DEX0337_103	31791	92877.02	76.5	29.4	38.5	0	445	504	443	502
DEX0337_104	33414	98977.01	76.5	29.4	38.5	0	569	628		
DEX0337_104	33414	98977.02	88.2	35.3	46.2	0	569	628		
DEX0337_105 DEX0337_106	33868	100639.01	52.9	23.5	30.8	0	465	524	465	524
DEX0337_105 DEX0337_106	33868	100639.02	76.5	17.6	23.1	0	465	524	465	524

#Data derived from lower PMT (550v) scans, all other data derived from standard (PMT 600v) scans. Under the original analysis at 600v scans, the data for these oligos did not reach the threshold for expression ratio.

5

Table 2. Sensitivity data for down-regulated genes.

DEX ID	Parent ID	OligoID	"%valid, n=17 *n=19"	"%up , n=17, *n=19"	"%up INV, n=13, *n=14"	"%up LMP, n=4, *n=5"	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0337_1	2111	5022	100*	31.6*	35.7*	20*	84	143		
DEX0337_2	3521	2311	100*	21.1*	14.3*	40*	91	150		
DEX0337_7	15229	23094.01	88.2	41.2	46.2	25	505	564		
DEX0337_7	15229	23094.02	88.2	35.3	38.5	25	505	564		
DEX0337_9 DEX0337_10	15337	13065.01	76.5	29.4	30.8	25	640	699	223	164
DEX0337_9 DEX0337_10	15337	13065.02	76.5	17.6	15.4	25	640	699	223	164
DEX0337_11 DEX0337_12	15382	22211.01	100	47.1	38.5	75	1110	1169	141	82

DEX ID	Parent ID	OligoID	"%valid, n=17 *n=19"	"%up , n=17, *n=19"	"%up INV, n=13, *n=14"	"%up LMP, n=4, *n=5"	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0337_11 DEX0337_12	15382	22211.02	100	52.9	46.2	75	1110	1169	141	82
DEX0337_15	15451	9282.01	94.1	29.4	30.8	25	764	823		
DEX0337_15	15451	9282.02	88.2	29.4	30.8	25	764	823		
DEX0337_17	15525	9420.01	70.6	17.6	7.7	50	784	843		
DEX0337_17	15525	9420.02	82.4	17.6	15.4	25	784	843		
DEX0337_18	15565	40563.01	94.1	47.1	53.8	25	166	225		
DEX0337_18	15565	40563.02	82.4	23.5	23.1	25	166	225		
DEX0337_19	15600	9364.01	94.1	29.4	23.1	50	390	449		
DEX0337_19	15600	9364.02	94.1	29.4	23.1	50	390	449		
DEX0337_20	15613	33308.01	82.4	23.5	30.8	0	24	83		
DEX0337_20	15613	33308.02	76.5	17.6	23.1	0	24	83		
DEX0337_21	15622	37055.01	94.1	35.3	30.8	50	280	339		
DEX0337_21	15622	37055.02	100	35.3	30.8	50	280	339		
DEX0337_28	15778	14694.01	100	94.1	92.3	100	364	423		
DEX0337_28	15778	14694.02	100	94.1	92.3	100	364	423		
DEX0337_30	15859	16267.01	100	52.9	46.2	75	428	487		
DEX0337_30	15859	16267.02	94.1	23.5	15.4	50	428	487		
DEX0337_38	16160	19484.01	100	29.4	30.8	25	547	606		
DEX0337_38	16160	19484.02	100	29.4	30.8	25	547	606		
DEX0337_39 DEX0337_40	16164	19522.01	58.8	29.4	23.1	50	276	335	1079	1137
DEX0337_39 DEX0337_40	16164	19522.02	100	64.7	53.8	100	276	335	1079	1137
DEX0337_41	16208	20317.01	100	29.4	30.8	25	317	376		
DEX0337_41	16208	20317.02	100	29.4	30.8	25	317	376		
DEX0337_49 DEX0337_50	16623	24670.01	88.2	23.5	30.8	0	586	645	145	86
DEX0337_49 DEX0337_50	16623	24670.02	94.1	29.4	30.8	25	586	645	145	86
DEX0337_51	16637	24778.01	100	23.5	30.8	0	349	408		
DEX0337_51	16637	24778.02	94.1	11.8	15.4	0	349	408		
DEX0337_52	16662	24972.01	100	47.1	46.2	50	1960	2019		
DEX0337_52	16662	24972.02	100	41.2	46.2	25	1960	2019		
DEX0337_53 DEX0337_54	16664	24982.01	100	35.3	38.5	25	2863	2922	2861	2920
DEX0337_53 DEX0337_54	16664	24982.02	100	47.1	53.8	25	2863	2922	2861	2920
DEX0337_57	16788	9924.01	76.5	23.5	15.4	50	861	920		
DEX0337_57	16788	9924.02	64.7	17.6	23.1	0	861	920		
DEX0337_67	16905	11259.01	94.1	47.1	46.2	50	5362	5421		
DEX0337_67	16905	11259.02	88.2	29.4	30.8	25	5362	5421		
DEX0337_68	16953	11461.01	100	17.6	7.7	50	609	668		
DEX0337_68	16953	11461.02	100	17.6	7.7	50	609	668		
DEX0337_70	16999	11625.01	100	70.6	84.6	25	5360	5419		
DEX0337_70	16999	11625.02	100	70.6	84.6	25	5360	5419		
DEX0337_71	17001	12139.01	100	41.2	46.2	25	1917	1976		
DEX0337_71	17001	12139.02	100	41.2	46.2	25	1917	1976		
DEX0337_72 DEX0337_73	17002	12143.01	100	23.5	30.8	0	3910	3969	6228	6287
DEX0337_72 DEX0337_73	17002	12143.02	100	17.6	23.1	0	3910	3969	6228	6287
DEX0337_76	26204	57229.01	100	29.4	23.1	50	506	565		
DEX0337_76	26204	57229.02	94.1	23.5	15.4	50	506	565		
DEX0337_78	26278	57425.01	82.4	5.9	7.7	0	730	789		
DEX0337_78	26278	57425.02	100	17.6	7.7	50	730	789		
DEX0337_79	26393	57681.01	100	17.6	15.4	25	724	783		
DEX0337_79	26393	57681.02	100	17.6	7.7	50	724	783		
DEX0337_80	26505	57829.01	100	17.6	15.4	25	213	272		
DEX0337_80	26505	57829.02	100	23.5	15.4	50	213	272		
DEX0337_81	26515	57857.01	100	23.5	15.4	50	510	569		
DEX0337_81	26515	57857.02	94.1	11.8	7.7	25	510	569		
DEX0337_83	26768	58557.01	100	23.5	23.1	25	319	378		
DEX0337_83	26768	58557.02	100	23.5	15.4	50	319	378		
DEX0337_86	27281	70124.01	100	29.4	23.1	50	1169	1228		
DEX0337_86	27281	70124.02	88.2	11.8	7.7	25	1169	1228		
DEX0337_87	27330	70292.01	100	58.8	53.8	75	447	506		

DEX ID	Parent ID	OligoID	"%valid, n=17 *n=19"	"%up , n=17, *n=19"	"%up INV, n=13, *n=14"	"%up LMP, n=4, *n=5"	Start Pos. Par. Seq	Stop Pos. Par. Seq	Start Pos. FLEXS	Stop Pos. FLEXS
DEX0337_87	27330	70292.02	100	58.8	53.8	75	447	506		
DEX0337_88	27363	70408.01	94.1	5.9	0	25	833	892		
DEX0337_88	27363	70408.02	94.1	11.8	0	50	833	892		

Table 3. Microarray Tissue Descriptions

Samples	Tissue ID		age of patient	description of tumor	grade	stage
OV.L.MU.478A1B	17478A1B	LMP	33	benign mucinous cystadenoma with focal proliferation	n/a	no
OV.I.SE370V	2370V	INV	47	invasive papillary serous adenocarcinoma	1-2	IV
OV.L1.SE105	S9822105	LMP	29	papillary serous carcinoma LMP	*0*	IC
OV.L.SE604A2B	14604A2B	LMP	64	serous cystadenofibroma of low malignant potential(Patient w/transitional cell carcinoma, in-situ and invasive of the bladder grade III/III)	n/a	no
OV.I.EN360	9410C360	INV	52	Endometrioid Adenocarcinoma, Stage Tx, Grade I/III	1-3	IV
OV.I.SE/EN005O	1005O	INV	60	Papillary serous and endometrioid ovarian carcinoma. Metastatic breast cancer, probable ovarian cancer	3	IV
OV.INV.SE.1040O	1040O	INV	67	papillary serous adenocarcinoma (Stage IV)	2	IV
OV.INV.SE.1071C	1071C	INV	51	papilary cystadenocarcinoma (Stage IV)	2	IV
OV.INV.MU.009	9507H009	INV	87	mucinous cystadenoma, multiloculated	N/A	
OV.LMP.MU.084	9808A084	LMP	47	mucinous borderline (LMP)	GB	
OV.INV.SE.291D01	VNM00291D01	INV	28	serous cystadenocarcinoma (Stage II)	1	II
OV.I.MU329D01	VNM00329D01	INV	40	mucinous cystadenocarcinoma	3	n/a
OV.INV.MX.010SP 1	9803G010SP1	INV	71	poorly diff. clear cell, endometrioid & serous papillary types (Stage IV)	4	III
OV.I.EN/MU.608A	95017608A	INV	56	endometrioid and mucinous adenocarcinoma	2	IV
OV.I.SE814V	1814V	INV	66	Papillary serous adenocarcinoma,	3-4	IV
OV.L.MU638A1C	14638A1C	LMP	26	mucinous cystic neoplasm of low malignant potential.	n/a	no
OV.I.SE/EN471A1B	14471A1B	INV	56	poorly differentiated adenocarcinoma with serous and endometroid features	3-4	IV
OV.INV.SE.693C	S995693A	INV	54	serous papillary carcinoma (Stage IV)	N/A	
OV.INV.SE.116D04	VNM00116D04	INV	47	cystaadenocarcinoma	1	

Example 3a: Alternative Splice Variants

We identified gene transcripts associated with cancer disease, development, or progression using cloning experiments, the Gencarta™ tools software (Compugen Ltd., Tel Aviv, Israel), and a variety of public and proprietary databases. These splice variants are either novel sequences which differ from a previously defined sequence or new uses of known sequences. In general the previously defined sequence for a family is annotated as DEX0443_XXX.nt.1 and the novel variants are annotated as DEX0443_XXX.nt.2,

DEX0443_XXX.nt.3, etc. The novel variant DNA sequences encode novel proteins which differ from a previously defined protein sequence. In relation to the nucleotide sequence naming convention, the previously defined amino acid sequence is annotated DEX0443_XXX.aa.1 and the novel variants annotated as DEX0443_XXX.aa.2, etc.

The mapping of the nucleic acid ("NT") SEQ ID NO; NT DEX ID; Parent NT ID, chromosomal location (if known); open reading frame (ORF) location; amino acid ("AA") SEQ ID NO, AA DEX ID, and Parent AA ID are shown in the table below.

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
1	DEX0443_001.nt.1	DEX0337_13, DEX0337_14	7p11.2	-	249	DEX0443_001.aa.1	DEX0337_113
2	DEX0443_001.nt.2	DEX0337_13, DEX0337_14	7p11.2				
3	DEX0443_002.nt.1	DEX0337_11, DEX0337_12	2q13	-	250	DEX0443_002.aa.1	DEX0337_112
4	DEX0443_002.nt.2	DEX0337_11, DEX0337_12	2q13				
5	DEX0443_002.nt.3	DEX0337_11, DEX0337_12	2q13	274-601	251	DEX0443_002.aa.3	
6	DEX0443_003.nt.1	DEX0337_35, DEX0337_36	*	-	252	DEX0443_003.aa.1	DEX0337_119
7	DEX0443_003.nt.2	DEX0337_35, DEX0337_36	*	-	253	DEX0443_003.aa.2	DEX0337_120
8	DEX0443_004.nt.1	DEX0337_34, DEX0337_45	9p24.3	-	254	DEX0443_004.aa.1	DEX0337_118
9	DEX0443_004.nt.2	DEX0337_34, DEX0337_45	9p24.3				
10	DEX0443_004.nt.3	DEX0337_34, DEX0337_45	9p24.3	2985-5847	255	DEX0443_004.aa.3	
11	DEX0443_004.nt.4	DEX0337_34, DEX0337_45	9p24.3	2962-5149	256	DEX0443_004.aa.4	
12	DEX0443_005.nt.1	DEX0337_60	2q24.3				
13	DEX0443_006.nt.1	DEX0337_58, DEX0337_59	*	-	257	DEX0443_006.aa.1	DEX0337_136
14	DEX0443_006.nt.2	DEX0337_58, DEX0337_59	*				
15	DEX0443_006.nt.3	DEX0337_58, DEX0337_59	*	295-514	258	DEX0443_006.aa.3	
16	DEX0443_006.nt.4	DEX0337_58, DEX0337_59	*	1-360	259	DEX0443_006.aa.4	
17	DEX0443_006.nt.5	DEX0337_58, DEX0337_59	*	265-649	260	DEX0443_006.aa.5	
18	DEX0443_006.nt.6	DEX0337_58, DEX0337_59	*	1-393	261	DEX0443_006.aa.6	
19	DEX0443_007.nt.1	DEX0337_7	4q28.1	-	262	DEX0443_007.aa.1	DEX0337_110
20	DEX0443_007.nt.2	DEX0337_7	4q28.1	1-584	263	DEX0443_007.aa.2	
21	DEX0443_008.nt.1	DEX0337_32	17p13.2	-	264	DEX0443_008.aa.1	DEX0337_116
22	DEX0443_009.nt.1	DEX0337_65	4q22.1	-	265	DEX0443_009.aa.1	DEX0337_139
23	DEX0443_010.nt.1	DEX0337_53, DEX0337_54	1p36.11	-	266	DEX0443_010.aa.1	DEX0337_132
24	DEX0443_010.nt.2	DEX0337_53, DEX0337_54	1p36.11				
25	DEX0443_011.nt.1	DEX0337_69	9q34.3	-	267	DEX0443_011.aa.1	DEX0337_141

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
26	DEX0443_011.nt.2	DEX0337_69	9q34.3	1-790	268	DEX0443_011.aa.2	
27	DEX0443_011.nt.3	DEX0337_69	9q34.3	1-1354	269	DEX0443_011.aa.3	
28	DEX0443_011.nt.4	DEX0337_69	9q34.3	1-1345	270	DEX0443_011.aa.4	
29	DEX0443_011.nt.5	DEX0337_69	9q34.3	2-410	271	DEX0443_011.aa.5	
30	DEX0443_011.nt.6	DEX0337_69	9q34.3	1-455	272	DEX0443_011.aa.6	
31	DEX0443_011.nt.7	DEX0337_69	9q34.3	1-685	273	DEX0443_011.aa.7	
32	DEX0443_012.nt.1	DEX0337_65	4q22.1	-	265	DEX0443_009.aa.1	DEX0337_139
33	DEX0443_012.nt.2	DEX0337_65	4q22.1	1-371	274	DEX0443_012.aa.2	
34	DEX0443_013.nt.1	DEX0337_8	12p13.2				
35	DEX0443_013.nt.2	DEX0337_8	12p13.2	-			
36	DEX0443_014.nt.1	DEX0337_33	7q11.21	-	275	DEX0443_014.aa.1	DEX0337_117
37	DEX0443_014.nt.2	DEX0337_33	7q11.21	608-959	276	DEX0443_014.aa.2	
38	DEX0443_014.nt.3	DEX0337_33	7q11.21	455-629	277	DEX0443_014.aa.3	
39	DEX0443_014.nt.4	DEX0337_33	7q11.21	1025-1460	278	DEX0443_014.aa.4	
40	DEX0443_015.nt.1	DEX0337_22, DEX0337_23	11p15.2				
41	DEX0443_015.nt.2	DEX0337_22, DEX0337_23	11p15.2				
42	DEX0443_015.nt.3	DEX0337_22, DEX0337_23	11p15.2	1-319	279	DEX0443_015.aa.3	
43	DEX0443_016.nt.1	DEX0337_71	1p21.3	-	280	DEX0443_016.aa.1	DEX0337_143
44	DEX0443_016.nt.2	DEX0337_71	1p21.3	215-419	281	DEX0443_016.aa.2	
45	DEX0443_016.nt.3	DEX0337_71	1p21.3	658-889	282	DEX0443_016.aa.3	
46	DEX0443_017.nt.1	DEX0337_18	21q21.1				
47	DEX0443_018.nt.1	DEX0337_20	3p14.1				
48	DEX0443_019.nt.1	DEX0337_21	6p22.3				
49	DEX0443_020.nt.1	DEX0337_61, DEX0337_62	*	-	283	DEX0443_020.aa.1	DEX0337_137
50	DEX0443_020.nt.2	DEX0337_61, DEX0337_62	*				
51	DEX0443_020.nt.3	DEX0337_61, DEX0337_62	*	243-633	284	DEX0443_020.aa.3	
52	DEX0443_020.nt.4	DEX0337_61, DEX0337_62	*	243-633	284	DEX0443_020.aa.3	
53	DEX0443_021.nt.1	DEX0337_49, DEX0337_50	2q32.2	-	285	DEX0443_021.aa.1	DEX0337_131
54	DEX0443_021.nt.2	DEX0337_49, DEX0337_50	2q32.2				

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
55	DEX0443_021.nt.3	DEX0337_49, DEX0337_50	2q32.2	609-1653	286	DEX0443_021.aa.3	
56	DEX0443_021.nt.4	DEX0337_49, DEX0337_50	2q32.2	1212-2256	286	DEX0443_021.aa.3	
57	DEX0443_021.nt.5	DEX0337_49, DEX0337_50	2q32.2	512-1496	287	DEX0443_021.aa.5	
58	DEX0443_021.nt.6	DEX0337_49, DEX0337_50	2q32.2	Jan-10	288	DEX0443_021.aa.6	
59	DEX0443_022.nt.1	DEX0337_44	1p36.11				
60	DEX0443_022.nt.2	DEX0337_44	1p36.11	1-250	289	DEX0443_022.aa.2	
61	DEX0443_022.nt.3	DEX0337_44	1p36.11	189-1272	290	DEX0443_022.aa.3	
62	DEX0443_022.nt.4	DEX0337_44	1p36.11	189-1590	291	DEX0443_022.aa.4	
63	DEX0443_022.nt.5	DEX0337_44	1p36.11	189-1176	292	DEX0443_022.aa.5	
64	DEX0443_022.nt.6	DEX0337_44	1p36.11	84-318	293	DEX0443_022.aa.6	
65	DEX0443_023.nt.1	DEX0337_56, DEX9000_058.nt.1, DEX9000_058.nt.2, DEX9000_058.nt.3	20p12.2	-	294	DEX0443_023.aa.1	DEX0337_134
66	DEX0443_023.nt.2	DEX0337_56, DEX9000_058.nt.1, DEX9000_058.nt.2, DEX9000_058.nt.3	20p12.2	-	295	DEX0443_023.aa.2	DEX9000_058.aa.1
67	DEX0443_023.nt.3	DEX0337_56, DEX9000_058.nt.1, DEX9000_058.nt.2, DEX9000_058.nt.3	20p12.2	-	296	DEX0443_023.aa.3	DEX9000_058.aa.2
68	DEX0443_023.nt.4	DEX0337_56, DEX9000_058.nt.1, DEX9000_058.nt.2, DEX9000_058.nt.3	20p12.2	-	297	DEX0443_023.aa.4	DEX9000_058.aa.4
69	DEX0443_023.nt.6	DEX0337_56, DEX9000_058.nt.1, DEX9000_058.nt.2, DEX9000_058.nt.3	20p12.2	604-1570	298	DEX0443_023.aa.6	
70	DEX0443_023.nt.7	DEX0337_56, DEX9000_058.nt.1, DEX9000_058.nt.2, DEX9000_058.nt.3	20p12.2	1-1123	299	DEX0443_023.aa.7	
71	DEX0443_024.nt.1	DEX0337_17	7p14.2				
72	DEX0443_025.nt.1	DEX0337_64	*	-	300	DEX0443_025.aa.1	DEX0337_138
73	DEX0443_026.nt.1	DEX0337_63	1q32.3				

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
74	DEX0443_026.nt.2	DEX0337_63	1q32.3	-			
75	DEX0443_026.nt.3	DEX0337_63	1q32.3	512-1361	301	DEX0443_026.aa.3	
76	DEX0443_027.nt.1	DEX0337_37	2p25.1	-	302	DEX0443_027.aa.1	DEX0337_121
77	DEX0443_028.nt.1	DEX0337_30, DEX0337_31	11q13.3	-	303	DEX0443_028.aa.1	DEX0337_115
78	DEX0443_028.nt.2	DEX0337_30, DEX0337_31	11q13.3				
79	DEX0443_028.nt.3	DEX0337_30, DEX0337_31	11q13.3	1172-1631	304	DEX0443_028.aa.3	
80	DEX0443_028.nt.4	DEX0337_30, DEX0337_31	11q13.3	1046-1505	304	DEX0443_028.aa.3	
81	DEX0443_029.nt.1	DEX0337_16	3q22.1				
82	DEX0443_029.nt.2	DEX0337_16	3q22.1	-			
83	DEX0443_030.nt.1	DEX0337_39, DEX0337_40	12p12.3	-	305	DEX0443_030.aa.1	DEX0337_123
84	DEX0443_030.nt.2	DEX0337_39, DEX0337_40	12p12.3	-	306	DEX0443_030.aa.2	DEX0337_124
85	DEX0443_030.nt.3	DEX0337_39, DEX0337_40	12p12.3	1-441	307	DEX0443_030.aa.3	
86	DEX0443_030.nt.4	DEX0337_39, DEX0337_40	12p12.3	1-564	308	DEX0443_030.aa.4	
87	DEX0443_030.nt.5	DEX0337_39, DEX0337_40	12p12.3	1-349	309	DEX0443_030.aa.5	
88	DEX0443_030.nt.6	DEX0337_39, DEX0337_40	12p12.3	1-450	310	DEX0443_030.aa.6	
89	DEX0443_030.nt.7	DEX0337_39, DEX0337_40	12p12.3	1-261	311	DEX0443_030.aa.7	
90	DEX0443_030.nt.8	DEX0337_39, DEX0337_40	12p12.3	1-345	312	DEX0443_030.aa.8	
91	DEX0443_030.nt.9	DEX0337_39, DEX0337_40	12p12.3	1-440	313	DEX0443_030.aa.9	
92	DEX0443_031.nt.1	DEX0337_19	8q23.1				
93	DEX0443_032.nt.1	DEX0337_37	2p25.1	-	302	DEX0443_027.aa.1	DEX0337_121
94	DEX0443_032.nt.2	DEX0337_37	2p25.1	1-1595	314	DEX0443_032.aa.2	
95	DEX0443_033.nt.1	DEX0337_72, DEX0337_73	13q14.11	-	315	DEX0443_033.aa.1	DEX0337_144
96	DEX0443_033.nt.2	DEX0337_72, DEX0337_73	13q14.11	-	316	DEX0443_033.aa.2	DEX0337_145
97	DEX0443_033.nt.3	DEX0337_72, DEX0337_73	13q14.11	1-495	317	DEX0443_033.aa.3	
98	DEX0443_034.nt.1	DEX0337_52	17q21.33				

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
99	DEX0443_034.nt.2	DEX0337_52	17q21.33	197-1281	318	DEX0443_034.aa.2	
100	DEX0443_035.nt.1	DEX0337_66	1q25.3	-	319	DEX0443_035.aa.1	DEX0337_140
101	DEX0443_036.nt.1	DEX0337_5, DEX0337_6	6q27	-	320	DEX0443_036.aa.1	DEX0337_109
102	DEX0443_036.nt.2	DEX0337_5, DEX0337_6	6q27				
103	DEX0443_036.nt.3	DEX0337_5, DEX0337_6	6q27	-			
104	DEX0443_037.nt.1	DEX0337_41	19p13.12	-	321	DEX0443_037.aa.1	DEX0337_125
105	DEX0443_037.nt.2	DEX0337_41	19p13.12	108-645	322	DEX0443_037.aa.2	
106	DEX0443_037.nt.3	DEX0337_41	19p13.12	108-675	323	DEX0443_037.aa.3	
107	DEX0443_037.nt.4	DEX0337_41	19p13.12	1-327	324	DEX0443_037.aa.4	
108	DEX0443_038.nt.1	DEX0337_98	*				
109	DEX0443_039.nt.1	DEX0337_68	6p21.31				
110	DEX0443_039.nt.2	DEX0337_68	6p21.31	1-753	325	DEX0443_039.aa.2	
111	DEX0443_039.nt.3	DEX0337_68	6p21.31	1-207	326	DEX0443_039.aa.3	
112	DEX0443_039.nt.4	DEX0337_68	6p21.31	1039-1705	327	DEX0443_039.aa.4	
113	DEX0443_039.nt.5	DEX0337_68	6p21.31	1-753	325	DEX0443_039.aa.2	
114	DEX0443_040.nt.1	DEX0337_51	8p12				
115	DEX0443_041.nt.1	DEX0337_3, DEX0337_4	1q23.3				
116	DEX0443_041.nt.10	DEX0337_3, DEX0337_4	1q23.3	599-926	328	DEX0443_041.aa.8	
117	DEX0443_041.nt.11	DEX0337_3, DEX0337_4	1q23.3	1-520	329	DEX0443_041.aa.11	
118	DEX0443_041.nt.12	DEX0337_3, DEX0337_4	1q23.3	497-1505	330	DEX0443_041.aa.12	
119	DEX0443_041.nt.13	DEX0337_3, DEX0337_4	1q23.3	497-1553	331	DEX0443_041.aa.13	
120	DEX0443_041.nt.14	DEX0337_3, DEX0337_4	1q23.3	1-753	332	DEX0443_041.aa.14	
121	DEX0443_041.nt.2	DEX0337_3, DEX0337_4	1q23.3	-	333	DEX0443_041.aa.2	DEX0337_108
122	DEX0443_041.nt.3	DEX0337_3, DEX0337_4	1q23.3	1-342	334	DEX0443_041.aa.3	
123	DEX0443_041.nt.4	DEX0337_3, DEX0337_4	1q23.3	1-664	335	DEX0443_041.aa.4	
124	DEX0443_041.nt.5	DEX0337_3, DEX0337_4	1q23.3	1-601	336	DEX0443_041.aa.5	

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
125	DEX0443_041.nt.6	DEX0337_3, DEX0337_4	1q23.3	2-320	337	DEX0443_041.aa.6	
126	DEX0443_041.nt.7	DEX0337_3, DEX0337_4	1q23.3	454-850	338	DEX0443_041.aa.7	
127	DEX0443_041.nt.8	DEX0337_3, DEX0337_4	1q23.3	599-926	328	DEX0443_041.aa.8	
128	DEX0443_041.nt.9	DEX0337_3, DEX0337_4	1q23.3	998-1325	328	DEX0443_041.aa.8	
129	DEX0443_042.nt.1	DEX0337_46, DEX0337_47	9p13.3	-	339	DEX0443_042.aa.1	DEX0337_128
130	DEX0443_042.nt.2	DEX0337_46, DEX0337_47	9p13.3	-	340	DEX0443_042.aa.2	DEX0337_129
131	DEX0443_042.nt.3	DEX0337_46, DEX0337_47	9p13.3	1-1106	341	DEX0443_042.aa.3	
132	DEX0443_042.nt.4	DEX0337_46, DEX0337_47	9p13.3	1-645	342	DEX0443_042.aa.4	
133	DEX0443_043.nt.1	DEX0337_48	4p16.3	-	343	DEX0443_043.aa.1	DEX0337_130
134	DEX0443_044.nt.1	DEX0337_55	2q37.3	-	344	DEX0443_044.aa.1	DEX0337_133
135	DEX0443_044.nt.2	DEX0337_55	2q37.3	1-1354	345	DEX0443_044.aa.2	
136	DEX0443_044.nt.3	DEX0337_55	2q37.3	1-1101	346	DEX0443_044.aa.3	
137	DEX0443_044.nt.4	DEX0337_55	2q37.3	Jan-71	347	DEX0443_044.aa.4	
138	DEX0443_045.nt.1	DEX0337_24, DEX0337_25	12q15	-	348	DEX0443_045.aa.1	DEX0337_114
139	DEX0443_045.nt.2	DEX0337_24, DEX0337_25	12q15				
140	DEX0443_046.nt.1	DEX0337_64	*	-	300	DEX0443_025.aa.1	DEX0337_138
141	DEX0443_046.nt.2	DEX0337_64	*	6-702	349	DEX0443_046.aa.2	
142	DEX0443_047.nt.1	DEX0337_10, DEX0337_9	4q27				
143	DEX0443_047.nt.2	DEX0337_10, DEX0337_9	4q27	-	350	DEX0443_047.aa.2	DEX0337_111
144	DEX0443_048.nt.1	DEX0337_1	9q21.12				
145	DEX0443_049.nt.1	DEX0337_42, DEX9000_052.nt.1, DEX9000_052.nt.2, DEX9000_052.nt.3	12p13.31	-	351	DEX0443_049.aa.1	DEX0337_126
146	DEX0443_049.nt.2	DEX0337_42, DEX9000_052.nt.1, DEX9000_052.nt.2, DEX9000_052.nt.3	12p13.31	-	352	DEX0443_049.aa.2	DEX9000_052.aa.1
147	DEX0443_049.nt.3	DEX0337_42, DEX9000_052.nt.1, DEX9000_052.nt.2, DEX9000_052.nt.3	12p13.31	-	353	DEX0443_049.aa.3	DEX9000_052.aa.2

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
148	DEX0443_049.nt.4	DEX0337_42, DEX9000_052.nt.1, DEX9000_052.nt.2, DEX9000_052.nt.3	12p13.31	-	354	DEX0443_049.aa.4	DEX9000_052.aa.3
149	DEX0443_049.nt.5	DEX0337_42, DEX9000_052.nt.1, DEX9000_052.nt.2, DEX9000_052.nt.3	12p13.31	248-2156	355	DEX0443_049.aa.5	
150	DEX0443_049.nt.6	DEX0337_42, DEX9000_052.nt.1, DEX9000_052.nt.2, DEX9000_052.nt.3	12p13.31	1-585	356	DEX0443_049.aa.6	
151	DEX0443_049.nt.7	DEX0337_42, DEX9000_052.nt.1, DEX9000_052.nt.2, DEX9000_052.nt.3	12p13.31	248-1166	357	DEX0443_049.aa.7	
152	DEX0443_050.nt.1	DEX0337_28	1p13.3				
153	DEX0443_051.nt.1	DEX0337_26, DEX0337_27	15q15.3				
154	DEX0443_051.nt.2	DEX0337_26, DEX0337_27	15q15.3				
155	DEX0443_051.nt.3	DEX0337_26, DEX0337_27	15q15.3	126-3510	358	DEX0443_051.aa.3	
156	DEX0443_051.nt.4	DEX0337_26, DEX0337_27	15q15.3	1-169	359	DEX0443_051.aa.4	
157	DEX0443_051.nt.5	DEX0337_26, DEX0337_27	15q15.3	1-221	360	DEX0443_051.aa.5	
158	DEX0443_052.nt.1	DEX0337_66	1q25.3	-	319	DEX0443_035.aa.1	DEX0337_140
159	DEX0443_053.nt.1	DEX0337_6	6q27				
160	DEX0443_054.nt.1	DEX0337_70	15q26.2	-	361	DEX0443_054.aa.1	DEX0337_142
161	DEX0443_055.nt.1	DEX0337_67	13q33.3				
162	DEX0443_055.nt.2	DEX0337_67	13q33.3	245-1067	362	DEX0443_055.aa.2	
163	DEX0443_055.nt.3	DEX0337_67	13q33.3	224-653	363	DEX0443_055.aa.3	
164	DEX0443_055.nt.4	DEX0337_67	13q33.3	245-1067	362	DEX0443_055.aa.2	
165	DEX0443_055.nt.5	DEX0337_67	13q33.3	245-1067	362	DEX0443_055.aa.2	
166	DEX0443_055.nt.6	DEX0337_67	13q33.3	245-1067	362	DEX0443_055.aa.2	
167	DEX0443_056.nt.1	DEX0337_77	*				
168	DEX0443_056.nt.2	DEX0337_77	*	-			
169	DEX0443_057.nt.1	DEX0337_15	6p22.3				

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
170	DEX0443_057.nt.2	DEX0337_15	6p22.3	178-487	364	DEX0443_057.aa.2	
171	DEX0443_057.nt.3	DEX0337_15	6p22.3	1-279	365	DEX0443_057.aa.3	
172	DEX0443_057.nt.4	DEX0337_15	6p22.3	178-661	366	DEX0443_057.aa.4	
173	DEX0443_057.nt.5	DEX0337_15	6p22.3	1-279	365	DEX0443_057.aa.3	
174	DEX0443_058.nt.1	DEX0337_38	6p21.31	-	367	DEX0443_058.aa.1	DEX0337_122
175	DEX0443_058.nt.2	DEX0337_38	6p21.31	34-214	368	DEX0443_058.aa.2	
176	DEX0443_058.nt.3	DEX0337_38	6p21.31	114-447	369	DEX0443_058.aa.3	
177	DEX0443_058.nt.4	DEX0337_38	6p21.31	1-187	370	DEX0443_058.aa.4	
178	DEX0443_059.nt.1	DEX0337_2	1q22				
179	DEX0443_059.nt.2	DEX0337_2	1q22	151-1358	371	DEX0443_059.aa.2	
180	DEX0443_059.nt.3	DEX0337_2	1q22	863-1595	372	DEX0443_059.aa.3	
181	DEX0443_059.nt.4	DEX0337_2	1q22	863-1595	372	DEX0443_059.aa.3	
182	DEX0443_060.nt.1	DEX0337_74	17q25.1				
183	DEX0443_060.nt.2	DEX0337_74	17q25.1	474-1617	373	DEX0443_060.aa.2	
184	DEX0443_060.nt.3	DEX0337_74	17q25.1	474-2514	374	DEX0443_060.aa.3	
185	DEX0443_060.nt.4	DEX0337_74	17q25.1	474-1617	373	DEX0443_060.aa.2	
186	DEX0443_060.nt.5	DEX0337_74	17q25.1	474-1617	373	DEX0443_060.aa.2	
187	DEX0443_060.nt.6	DEX0337_74	17q25.1	176-548	375	DEX0443_060.aa.6	
188	DEX0443_060.nt.7	DEX0337_74	17q25.1	1-289	376	DEX0443_060.aa.7	
189	DEX0443_061.nt.1	DEX0337_43	9q22.32				
190	DEX0443_061.nt.2	DEX0337_43	9q22.32	838-1043	377	DEX0443_061.aa.2	
191	DEX0443_062.nt.1	DEX0337_57	*	-	378	DEX0443_062.aa.1	DEX0337_135
192	DEX0443_062.nt.2	DEX0337_57	*	1-212	379	DEX0443_062.aa.2	
193	DEX0443_063.nt.1	DEX0337_82					
194	DEX0443_064.nt.1	DEX0337_71		-	380	DEX0443_064.aa.1	DEX0337_143
195	DEX0443_065.nt.1	DEX0337_95					
196	DEX0443_066.nt.1	DEX0337_72		-	381	DEX0443_066.aa.1	DEX0337_144
197	DEX0443_066.nt.2	DEX0337_73		-	382	DEX0443_066.aa.2	DEX0337_145
198	DEX0443_067.nt.1	DEX0337_33		-	383	DEX0443_067.aa.1	DEX0337_117
199	DEX0443_068.nt.1	DEX0337_96					
200	DEX0443_069.nt.1	DEX0337_93					

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
201	DEX0443_070.nt.1	DEX0337_99					
202	DEX0443_071.nt.1	DEX0337_57		-	384	DEX0443_071.aa.1	DEX0337_135
203	DEX0443_072.nt.1	DEX0337_100					
204	DEX0443_073.nt.1	DEX0337_83					
205	DEX0443_074.nt.1	DEX0337_76					
206	DEX0443_075.nt.1	DEX0337_69		-	385	DEX0443_075.aa.1	DEX0337_141
207	DEX0443_076.nt.1	DEX0337_7		-	386	DEX0443_076.aa.1	DEX0337_110
208	DEX0443_077.nt.1	DEX0337_42		-	387	DEX0443_077.aa.1	DEX0337_126
209	DEX0443_078.nt.1	DEX0337_87					
210	DEX0443_079.nt.1	DEX0337_85					
211	DEX0443_080.nt.1	DEX0337_92					
212	DEX0443_081.nt.1	DEX0337_48		-	388	DEX0443_081.aa.1	DEX0337_130
213	DEX0443_082.nt.1	DEX0337_2					
214	DEX0443_083.nt.1	DEX0337_81					
215	DEX0443_084.nt.1	DEX0337_43					
216	DEX0443_085.nt.1	DEX0337_75					
217	DEX0443_086.nt.1	DEX0337_86					
218	DEX0443_087.nt.1	DEX0337_60					
219	DEX0443_088.nt.1	DEX0337_79					
220	DEX0443_089.nt.1	DEX0337_94					
221	DEX0443_090.nt.1	DEX0337_74					
222	DEX0443_091.nt.1	DEX0337_1					
223	DEX0443_092.nt.1	DEX0337_28					
224	DEX0443_093.nt.1	DEX0337_32		-	389	DEX0443_093.aa.1	DEX0337_116
225	DEX0443_094.nt.1	DEX0337_65		-	390	DEX0443_094.aa.1	DEX0337_139
226	DEX0443_095.nt.1	DEX0337_64		-	391	DEX0443_095.aa.1	DEX0337_138
227	DEX0443_096.nt.1	DEX0337_97					
228	DEX0443_097.nt.1	DEX0337_58		-	392	DEX0443_097.aa.1	DEX0337_136
229	DEX0443_097.nt.2	DEX0337_59					
230	DEX0443_098.nt.1	DEX0337_89					
231	DEX0443_099.nt.1	DEX0337_101					
232	DEX0443_100.nt.1	DEX0337_35		-	393	DEX0443_100.aa.1	DEX0337_119
233	DEX0443_101.nt.1	DEX0337_98					
234	DEX0443_102.nt.1	DEX0337_40		-	394	DEX0443_102.aa.1	DEX0337_124
235	DEX0443_102.nt.2	DEX0337_39		-	395	DEX0443_102.aa.2	DEX0337_123
236	DEX0443_103.nt.1	DEX0337_84					
237	DEX0443_104.nt.1	DEX0337_77					
238	DEX0443_105.nt.1	DEX0337_80					
239	DEX0443_106.nt.1	DEX0337_45					
240	DEX0443_107.nt.1	DEX0337_18					
241	DEX0443_108.nt.1	DEX0337_27					
242	DEX0443_109.nt.1	DEX0337_24		-	396	DEX0443_109.aa.1	DEX0337_114
243	DEX0443_109.nt.2	DEX0337_25					

SEQ ID NO	NT DEX ID	Parent NT ID	Chromo Map	ORF Loc	SEQ ID NO	AA DEX ID	Parent AA ID
244	DEX0443_110.nt.1	DEX0337_88					
245	DEX0443_111.nt.1	DEX0337_90					
246	DEX0443_112.nt.1	DEX0337_29					
247	DEX0443_113.nt.1	DEX0337_78					
248	DEX0443_114.nt.1	DEX0337_91					

EST Support

The alternative splice variants were predicted by computational analysis of Expressed Sequence Tags (ESTs) derived form public and proprietary cDNA libraries and genomic information.

SAGE Support

Serial Analysis of Gene Expression (SAGE) tag data analysis is preformed on the splice variants. Gencarta™ tools (Compugen Ltd., Tel Aviv, Israel) report SAGE tag data for individual transcripts when available. SAGE data includes the SAGE tag sequence for the transcript, expression level (as a ratio) of the SAGE tag in tissue samples, the source or tissue, state or disease condition of the tissue, tissue sample type, and a description of the tissue samples.

Sequence Alignment Support

Alignments of previously identified reference sequences and novel splice variant sequences are performed to confirm unique portions of splice variant nucleic acid and amino acid sequences. The alignments are done using the Needle program in the European Molecular Biology Open Software Suite (EMBOSS) version 2.2.0 available at www.emboss.org from EMBnet (http://www.embnet.org). Default settings are used unless otherwise noted. The Needle program in EMBOSS implements the Needleman-Wunsch algorithm. Needleman, S. B., Wunsch, C. D., *J. Mol. Biol.* 48:443-453 (1970).

It is well know to those skilled in the art that implication of alignment algorithms by various programs may result in minor changes in the generated output. These changes include but are not limited to: alignment scores (percent identity, similarity, and gap), display of nonaligned flanking sequence regions, and number assignment to residues. These minor changes in the output of an alignment do not alter the physical characteristics of the sequences or the differences between the sequences, e.g. regions of homology, insertions, or deletions. Descriptions of alignments are provided in each splice variant section below.

Splice Variant Polypeptide Annotation

The polypeptides of the present invention were analyzed and the following attributes were identified; specifically, epitopes, post translational modifications, signal

peptides and transmembrane domains. Antigenicity (Epitope) prediction was performed through the antigenic module in the EMBOSS package. Rice, P., EMBOSS: The European Molecular Biology Open Software Suite, *Trends in Genetics* 16(6): 276-277 (2000). The antigenic module predicts potentially antigenic regions of a protein sequence, using the method of Kolaskar and Tongaonkar. Kolaskar, AS and Tongaonkar, PC., A semi-empirical method for prediction of antigenic determinants on protein antigens, *FEBS Letters* 276: 172-174 (1990). Examples of post-translational modifications (PTMs) and other motifs of the OSPs of this invention are listed below. In addition, antibodies that specifically bind such post-translational modifications may be useful as a diagnostic or as therapeutic. The PTMs and other motifs were predicted by using the ProSite Dictionary of Proteins Sites and Patterns (Bairoch *et al.*, *Nucleic Acids Res.* 25(1):217-221 (1997)), the following motifs, including PTMs, were predicted for the OSPs of the invention. The signal peptides were detected by using the SignalP 2.0, *see* Nielsen *et al.*, *Protein Engineering* 12, 3-9 (1999). Prediction of transmembrane helices in proteins was performed by the application TMHMM 2.0, "currently the best performing transmembrane prediction program", according to authors (Krogh *et al.*, *Journal of Molecular Biology*, 305(3):567-580, (2001); Moller *et al.*, *Bioinformatics*, 17(7):646-653, (2001); Sonnhammer, *et al.*, *A hidden Markov model for predicting transmembrane helices in protein sequences* in Glasgow, *et al.* Ed. Proceedings of the Sixth International Conference on Intelligent Systems for Molecular Biology, pages 175-182, Menlo Park, CA, 1998. AAAI Press. The PSORT II program may also be used to predict cellular localizations. Horton et al., *Intelligent Systems for Molecular Biology* 5: 147-152 (1997). The table below includes the following sequence annotations: Signal peptide presence; TM (number of membrane domain, topology in orientation and position); Amino acid location and antigenic index (location, AI score, length); PTM and other motifs (type, amino acid residue locations); and functional domains.

AA SEQ ID	Sig P	TMHMM	Antigenicity	PTM	Domain
DEX0443_001.aa.1	Y	0 - o	4-25,1.252		
DEX0443_002.aa.1	y	0 - i	70-79,1.158; 94-105,1.153; 17-55,1.125; 59-67,1.082	Myristyl 62-67, 77-82, 87-92, 91-96, 94-99; Pkc_Phospho_Site 12-14; Prokar_Lipoprotein 68-78;	
DEX0443_002.aa.3	y	0 - i	70-79,1.158; 94-105,1.153; 17-55,1.125; 59-67,1.082	Myristyl 62-67, 77-82, 87-92, 91-96, 94-99; Pkc_Phospho_Site 12-14;	

				Prokar_Lipoprotein 68-78;	
DEX0443_003.aa.1	N	0 - o	51-60,1.178; 62-68,1.130; 30-45,1.109	Asn_Glycosylation 19-22; Ck2_Phospho_Site 60-63, 64-67; Myristyl 17-22, 41-46, 54-59; Pkc_Phospho_Site 47-49;	Lipocalin-related protein and Bos/Can/Equ allergen
DEX0443_003.aa.2	N	0 - o	4-15,1.178; 58-67,1.178; 69-81,1.149; 105-114,1.123; 94-100,1.080; 37-52,1.076	Asn_Glycosylation 26-29; Ck2_Phospho_Site 67-70, 71-74; Myristyl 24-29, 48-53, 61-66; Pkc_Phospho_Site 54-56, 89-91, 118-120;	Lipocalin-related protein and Bos/Can/Equ allergen
DEX0443_004.aa.1	N	0 - o	52-62,1.259; 16-24,1.148; 191-210,1.133; 151-159,1.116; 6-14,1.107; 33-39,1.106; 90-100,1.098; 161-166,1.073; 118-128,1.067; 104-110,1.059; 79-86,1.058; 225-231,1.043	Asn_Glycosylation 29-32, 144-147, 171-174, 174-177, 207-210; Ck2_Phospho_Site 35-38, 64-67, 100-103, 164-167, 176-179; Glycosaminoglycan 31-34; Myristyl 59-64; Pkc_Phospho_Site 21-23, 64-66, 223-225, 236-238;	
DEX0443_004.aa.3	N	5 - i21-43o56-78i189-211o266 - 288i295 -317o	141-213,1.251; 753-782,1.251; 570-587,1.245; 52-80,1.244; 655-680,1.230; 292-319,1.220; 21-46,1.201; 531-544,1.196; 624-652,1.188; 121-132,1.185; 884-898,1.185; 787-805,1.180; 818-881,1.176; 589-601,1.168; 348-380,1.166; 609-619,1.166; 721-739,1.162; 99-116,1.162; 512-524,1.154; 255-286,1.151; 321-340,1.148; 409-462,1.144; 492-507,1.141; 924-935,1.123; 243-252,1.116; 4-19,1.116; 84-92,1.108; 388-401,1.100; 551-568,1.095; 914-920,1.094; 691-697,1.081; 810-816,1.062; 700-708,1.061	Asn_Glycosylation 56-59, 233-236, 746-749, 752-755, 787-790; Ck2_Phospho_Site 508-511, 551-554, 702-705, 719-722, 884-887, 909-912, 939-942, 941-944; Myristyl 135-140, 245-250, 656-661, 700-705; Pkc_Phospho_Site 3-5, 144-146, 166-168, 235-237, 264-266, 322-324, 337-339, 356-358, 551-553, 627-629, 721-723, 760-762, 789-791, 813-815, 840-842, 884-886, 909-911, 914-916, 917-919, 943-945; Tyr_Phospho_Site 302-308; Prokar_Lipoprotein 664-674;	
DEX0443_004.aa.4	N	6 - o130-149i169 - 191o206 - 228i340	292-364,1.251; 203-243,1.244; 126-152,1.243; 443-470,1.220; 172-197,1.201; 74-83,1.196; 9-27,1.196;	Asn_Glycosylation 125-128, 207-210, 384-387; Ck2_Phospho_Site 37-40, 118-121, 659-662, 684-687, 714-717,	

		- 362o417 - 439i446 -468o	250-283,1.185; 659-673,1.185; 94-120,1.182; 38-69,1.174; 499-531,1.166; 406-437,1.151; 472-491,1.148; 560-613,1.144; 699-710,1.123; 643-656,1.122; 394-403,1.116; 162-170,1.116; 538-552,1.100; 689-695,1.094; 154-160,1.051	716-719; Myristyl 286-291, 396-401; Pkc_Phospho_Site 7-9, 95-97, 158-160, 295-297, 317-319, 386-388, 415-417, 473-475, 488-490, 507-509, 659-661, 684-686, 689-691, 692-694, 718-720; Tyr_Phospho_Site 453-459;	
DEX0443_006.aa.1	N	0 - o	140-148,1.140; 4-21,1.126; 52-70,1.119; 37-46,1.108; 74-87,1.101; 111-121,1.089; 100-107,1.088; 93-98,1.082; 123-132,1.074	Amidation 140-143; Asn_Glycosylation 34-37, 95-98; Ck2_Phospho_Site 64-67; Glycosaminoglycan 53-56; Myristyl 44-49, 98-103, 137-142; Pkc_Phospho_Site 74-76, 133-135;	
DEX0443_006.aa.3	N	0 - o	36-61,1.137; 20-26,1.110	Asn_Glycosylation 70-73; Ck2_Phospho_Site 5-8, 9-12, 34-37, 49-52, 66-69;	
DEX0443_006.aa.4	N	0 - o	94-113,1.218; 38-54,1.123; 26-32,1.099; 71-78,1.079; 84-89,1.031	Asn_Glycosylation 39-42; Ck2_Phospho_Site 7-10, 13-16, 41-44, 63-66, 74-77; Pkc_Phospho_Site 74-76;	
DEX0443_006.aa.5	Y	0 - o	4-25,1.193; 77-90,1.180; 109-124,1.117; 43-58,1.096; 60-65,1.063; 28-36,1.061	Ck2_Phospho_Site 16-19, 82-85; Myristyl 116-121;	
DEX0443_006.aa.6	N	0 - o	94-105,1.208; 28-46,1.188; 78-85,1.142; 117-127,1.097; 60-74,1.085	Amidation 9-12; Asn_Glycosylation 63-66; Ck2_Phospho_Site 61-64, 113-116; Pkc_Phospho_Site 52-54; Aa_Trna_Ligase_I i_1 27-49;	Aminoacyl-transfer RNA synthetases class-II
DEX0443_007.aa.1	N	0 - i	21-29,1.168; 63-80,1.159; 103-111,1.144; 82-96,1.123; 148-157,1.113; 54-60,1.086; 135-143,1.070; 125-133,1.062	Amidation 9-12; Camp_Phospho_Site 13-16; Ck2_Phospho_Site 149-152; Myristyl 79-84, 88-93; Pkc_Phospho_Site 20-22, 59-61, 67-69, 74-76, 149-151; Ribosomal_L21e 43-68;	Ribosomal protein L21E
DEX0443_007.aa.2	Y	1 - i30-52o	146-164,1.228; 166-191,1.222; 39-67,1.208; 116-133,1.183; 75-85,1.175;	Asn_Glycosylation 93-96, 117-120, 141-144; Ck2_Phospho_Site 58-61; Myristyl	

			9-34,1.171; 100-114,1.115	42-47, 138-143; Pkc_Phospho_Site 146-148, 176-178;	
DEX0443_008.aa.1	N	0 - 0	50-67,1.164; 35-48,1.140; 4-12,1.093; 16-22,1.087	Ck2_Phospho_Site 15-18;	
DEX0443_009.aa.1	N	0 - 0	71-83,1.182; 90-97,1.134; 211-219,1.127; 130-141,1.117; 186-193,1.076; 59-65,1.067; 195-202,1.065; 226-240,1.059; 169-177,1.041	Asn_Glycosylation 13-16, 40-43; Ck2_Phospho_Site 119-122, 125-128, 149-152, 162-165, 214-217, 225-228; Myristyl 134-139; Pkc_Phospho_Site 105-107, 173-175; Rgd 93-95; Tyr_Phospho_Site 109-115;	Osteopontin; NULL
DEX0443_010.aa.1	y	0 - 0	4-37,1.173; 44-55,1.085	Ck2_Phospho_Site 15-18;	
DEX0443_011.aa.1	N	0 - 0	23-35,1.178; 213-239,1.178; 140-168,1.155; 241-249,1.130; 290-299,1.123; 195-211,1.089; 279-285,1.080; 57-71,1.076; 100-106,1.070; 170-176,1.068; 79-89,1.060; 8-15,1.052; 261-266,1.025	Asn_Glycosylation 19-22, 46-49, 137-140; Ck2_Phospho_Site 77-80, 139-142, 239-242, 243-246; Myristyl 15-20, 44-49, 68-73, 92-97, 97-102, 101-106, 115-120, 233-238; Pkc_Phospho_Site 74-76, 77-79, 119-121, 188-190, 212-214, 274-276, 303-305;	Lipocalin-related protein and Bos/Can/Equ allergen; Lipocalin
DEX0443_011.aa.2	y	0 - 0	45-70,1.189; 97-109,1.178; 187-196,1.178; 15-38,1.169; 198-206,1.130; 247-256,1.123; 236-242,1.080; 131-145,1.076; 174-180,1.070; 6-12,1.064; 153-163,1.060; 82-89,1.052; 218-223,1.025	Asn_Glycosylation 93-96, 120-123; Ck2_Phospho_Site 151-154, 196-199, 200-203; Myristyl 89-94, 118-123, 142-147, 166-171, 171-176, 175-180, 186-191, 190-195; Pkc_Phospho_Site 7-9, 148-150, 151-153, 231-233, 260-262; Lipocalin 75-88;	Lipocalin-related protein and Bos/Can/Equ allergen
DEX0443_011.aa.3	N	0 - 0	45-70,1.189; 320-332,1.178; 375-384,1.178; 15-38,1.169; 386-394,1.130; 435-444,1.123; 178-185,1.121; 132-150,1.107; 230-238,1.082; 424-430,1.080; 354-369,1.076; 108-114,1.075; 97-102,1.067; 268-277,1.065; 6-12,1.064;	Amidation 128-131, 298-301; Asn_Glycosylation 268-271, 316-319, 343-346; Ck2_Phospho_Site 219-222, 384-387, 388-391; Glycosaminoglycan 287-290; Myristyl 104-109, 121-126, 196-201, 210-215, 212-217, 213-218, 228-	Lipocalin-related protein and Bos/Can/Equ allergen; Lipocalin; Prostaglandin D synthase

			305-312,1.052; 255-261,1.049; 87-93,1.037; 166-172,1.033; 406-411,1.025	233, 232-237, 278-283, 298-303, 312-317, 341-346, 365-370, 378-383; Pkc_Phospho_Site 7-9, 88-90, 100-102, 110-112, 125-127, 204-206, 258-260, 371-373, 419-421, 448-450; Lipocalin 298-311, 299-311;	
DEX0443_01 1.aa.4	N	0 - o	418-433,1.295; 263-275,1.199; 45-70,1.189; 15-38,1.169; 200-209,1.156; 159-172,1.150; 407-413,1.106; 397-405,1.106; 382-388,1.103; 219-225,1.098; 436-444,1.088; 318-325,1.078; 108-114,1.075; 132-149,1.075; 345-354,1.074; 329-335,1.068; 97-102,1.067; 6-12,1.064; 237-242,1.056; 87-93,1.037; 246-252,1.033	Amidation 128-131, 231-234, 327-330, 381-384; Camp_Phospho_Site 233-236; Ck2_Phospho_Site 261-264; Myristyl 104-109, 121-126, 190-195, 195-200, 198-203, 200-205, 228-233, 280-285, 288-293, 290-295, 292-297, 293-298, 306-311, 316-321, 324-329, 341-346, 346-351, 360-365, 364-369, 368-373, 372-377, 378-383; Pkc_Phospho_Site 7-9, 88-90, 100-102, 110-112, 125-127, 178-180, 184-186, 220-222, 231-233, 248-250;	NULL
DEX0443_01 1.aa.5	Y	0 - o	46-89,1.223; 8-36,1.181; 120-129,1.123; 109-115,1.080; 38-44,1.052	Asn_Glycosylation 98-101; Myristyl 26-31, 59-64, 76-81; Pkc_Phospho_Site 104-106, 133-135; Prokar_Lipoprotein 50-60;	Lipocalin-related protein and Bos/Can/Equ allergen
DEX0443_01 1.aa.6	N	0 - o	75-102,1.154; 11-27,1.137; 110-116,1.090; 38-45,1.081; 47-53,1.067; 137-147,1.065	Asn_Glycosylation 76-79; Ck2_Phospho_Site 51-54; Myristyl 56-61, 67-72, 70-75, 74-79, 79-84, 110-115, 120-125, 143-148; Pkc_Phospho_Site 38-40, 121-123;	
DEX0443_01 1.aa.7	N	0 - o	45-70,1.189; 97-109,1.178; 152-161,1.178; 15-38,1.169; 163-171,1.130; 212-221,1.123; 201-207,1.080; 131-146,1.076; 6-12,1.064; 82-89,1.052;	Asn_Glycosylation 93-96, 120-123; Ck2_Phospho_Site 161-164, 165-168; Myristyl 89-94, 118-123, 142-147, 155-160; Pkc Phospho Site	Lipocalin-related protein and Bos/Can/Equ allergen; Lipocalin; Prostaglandin D synthase

			183-188,1.025	7-9, 148-150, 196-198, 225-227; Lipocalin 75-88;	
DEX0443_012.aa.2	N	0 - o	113-119,1.127; 32-43,1.117; 88-95,1.076; 97-104,1.065; 71-79,1.049	Ck2_Phospho_Site 5-8, 21-24, 27-30, 51-54, 64-67, 116-119; Myristyl 36-41; Pkc_Phospho_Site 75-77;	
DEX0443_014.aa.1	N	0 - o	4-11,1.149; 45-54,1.095; 29-34,1.048	Asn_Glycosylation 24-27; Camp_Phospho_Site 42-45; Ck2_Phospho_Site 26-29, 54-57; Myristyl 19-24, 50-55;	Aminopeptidase N, APN (CD13)
DEX0443_014.aa.2	N	0 - o	69-80,1.147; 4-13,1.110; 27-37,1.085; 50-61,1.080; 82-89,1.049	Amidation 44-47; Camp_Phospho_Site 53-56, 59-62; Ck2_Phospho_Site 41-44; Pkc_Phospho_Site 48-50, 52-54, 57-59, 62-64, 102-104, 106-108;	
DEX0443_014.aa.3	N	0 - o	35-53,1.229; 9-19,1.088; 22-32,1.087	Asn_Glycosylation 56-59; Ck2_Phospho_Site 23-26; Tyr_Phospho_Site 32-40;	
DEX0443_014.aa.4	N	0 - o	87-110,1.192; 4-14,1.156; 53-64,1.118; 44-50,1.089; 76-82,1.081; 117-125,1.081; 67-74,1.056	Camp_Phospho_Site 22-25;	
DEX0443_015.aa.3	y	0 - o	27-34,1.140; 4-11,1.096; 16-22,1.068; 38-44,1.033	Amidation 52-55; Asn_Glycosylation 60-63; Camp_Phospho_Site 84-87; Ck2_Phospho_Site 87-90; Glycosaminoglycan 42-45; Myristyl 43-48; Pkc_Phospho_Site 63-65;	
DEX0443_016.aa.1	Y	1 - o252-274i	251-283,1.275; 216-228,1.194; 180-192,1.149; 61-71,1.145; 6-32,1.142; 96-114,1.119; 172-178,1.104; 142-160,1.096; 38-43,1.087; 236-242,1.071; 79-84,1.064; 88-94,1.049	Tissue_Factor 82-99; Amidation 200-203; Asn_Glycosylation 48-51, 161-164, 174-177; Camp_Phospho_Site 237-240; Ck2_Phospho_Site 58-61, 90-93, 92-95, 125-128, 163-166, 179-182, 242-245, 290-293; Myristyl 36-41, 39-44, 118-123, 157-162, 248-253, 286-291; Pkc_Phospho_Site	Cytokine receptor class 2 family; Tissue Factor (TF)

				50-52, 76-78, 179-181, 200-202, 204-206, 290-292;	
DEX0443_016.aa.2	Y	0 - o	52-64,1.179; 42-49,1.142; 6-33,1.142	Glycosaminoglycan 38-41; Myristyl 39-44, 43-48, 47-52;	
DEX0443_016.aa.3	Y	1 - i21-43o	4-44,1.209; 61-73,1.179; 51-58,1.142	Myristyl 5-10, 39-44, 48-53, 52-57, 56-61; Pkc_Phospho_Site 13-15;	
DEX0443_020.aa.1	N	0 - o	14-47,1.175; 76-98,1.143; 119-126,1.128; 49-57,1.127; 109-116,1.077; 101-107,1.061; 6-12,1.051; 66-73,1.035	Myristyl 107-112; Pkc_Phospho_Site 27-29, 51-53;	
DEX0443_020.aa.3	N	0 - o	14-47,1.175; 76-98,1.143; 119-126,1.128; 49-57,1.127; 109-116,1.077; 101-107,1.061; 6-12,1.051; 66-73,1.035	Myristyl 107-112; Pkc_Phospho_Site 27-29, 51-53;	
DEX0443_021.aa.1	Y	0 - o	4-20,1.253; 22-31,1.067	Asn_Glycosylation 53-56; Ck2_Phospho_Site 23-26; Myristyl 51-56;	
DEX0443_021.aa.3	N	3 - o47-69i215-237o252-270i	11-83,1.303; 208-289,1.280; 117-193,1.233; 293-319,1.228; 86-110,1.216; 4-9,1.137; 200-206,1.064	Myristyl 136-141;	NULL
DEX0443_021.aa.5	Y	0 - o	4-32,1.295; 103-115,1.061; 160-169,1.056; 205-221,1.055; 79-85,1.048; 301-308,1.028; 233-241,1.010	Ck2_Phospho_Site 23-26, 174-177; Myristyl 101-106, 119-124, 170-175, 182-187, 194-199, 293-298; Pkc_Phospho_Site 148-150; Rgd 259-261;	Collagen triple helix repeat; Proline-rich region; NULL
DEX0443_021.aa.6	N	0 - o	646-660,1.144; 628-641,1.128; 544-554,1.110; 692-699,1.106; 605-617,1.081; 569-594,1.071; 255-261,1.068; 486-496,1.063; 202-211,1.049; 45-60,1.049; 436-445,1.049; 151-159,1.048; 112-118,1.036; 670-676,1.030; 375-381,1.025; 682-689,1.023; 174-187,1.022; 12-27,1.022; 535-540,1.017; 133-139,1.010; 511-520,1.010; 327-333,1.001	Ck2_Phospho_Site 275-278, 362-365, 559-562, 612-615, 683-686; Myristyl 118-123, 121-126, 124-129, 127-132, 130-135, 151-156, 163-168, 196-201, 214-219, 232-237, 262-267, 283-288, 349-354, 432-437, 448-453, 453-458, 475-480, 499-504, 511-516, 541-546, 563-568; Pkc_Phospho_Site 39-41, 366-368, 546-548, 559-561, 588-590,	Collagen triple helix repeat; Proline-rich region; Fibrillar collagen C-terminal domain; Gram-positive cocci surface protein 'anchoring' hexapeptide; NULL

				605-607, 612-614; Gram_Pos_Anchoring 449-454;	
DEX0443_022.aa.2	N	0 - o	4-11,1.131; 15-23,1.096; 45-51,1.090	Glycosaminoglycan 81-84;	
DEX0443_022.aa.3	N	0 - o	239-267,1.186; 13-34,1.181; 209-218,1.167; 309-318,1.162; 179-186,1.153; 73-108,1.131; 290-300,1.120; 121-147,1.118; 4-10,1.110; 193-199,1.098; 169-175,1.090; 112-119,1.083; 46-55,1.071; 341-347,1.071	Amidation 222-225, 330-333; Asn_Glycosylation 113-116; Camp_Phospho_Site 83-86; Ck2_Phospho_Site 23-26, 49-52; Myristyl 195-200, 208-213, 268-273; Pkc_Phospho_Site 53-55, 61-63;	NAD dependent epimerase/dehydratase family
DEX0443_022.aa.4	N	0 - o	337-393,1.213; 239-267,1.186; 399-417,1.182; 13-34,1.181; 209-218,1.167; 309-318,1.162; 179-186,1.153; 422-434,1.145; 73-108,1.131; 290-300,1.120; 121-147,1.118; 4-10,1.110; 193-199,1.098; 169-175,1.090; 112-119,1.083; 46-55,1.071	Amidation 222-225, 330-333; Asn_Glycosylation 113-116; Camp_Phospho_Site 83-86; Ck2_Phospho_Site 23-26, 49-52; Glycosaminoglycan 465-468; Myristyl 195-200, 208-213, 268-273, 364-369; Pkc_Phospho_Site 53-55, 61-63, 351-353, 377-379, 404-406;	NAD dependent epimerase/dehydratase family
DEX0443_022.aa.5	N	0 - o	239-267,1.186; 13-34,1.181; 209-218,1.167; 309-318,1.162; 179-186,1.153; 73-108,1.131; 290-300,1.120; 121-147,1.118; 4-10,1.110; 193-199,1.098; 169-175,1.090; 112-119,1.083; 46-55,1.071	Amidation 222-225; Asn_Glycosylation 113-116; Camp_Phospho_Site 83-86; Ck2_Phospho_Site 23-26, 49-52; Myristyl 195-200, 208-213, 268-273; Pkc_Phospho_Site 53-55, 61-63;	NAD dependent epimerase/dehydratase family
DEX0443_022.aa.6	N	0 - o	59-74,1.132; 11-37,1.118		
DEX0443_023.aa.1	N	1 - o236-258i	235-261,1.187; 165-177,1.167; 5-24,1.165; 196-228,1.160; 63-84,1.157; 138-147,1.152; 96-124,1.126; 46-52,1.097; 179-193,1.083; 154-160,1.064	Asn_Glycosylation 40-43, 58-61, 132-135; Ck2_Phospho_Site 46-49, 107-110; Myristyl 247-252; Pkc_Phospho_Site 140-142, 153-155; Lamp_1 61-75;	Lysosome-associated membrane glycoprotein (Lamp)/CD68
DEX0443_023.aa.2	y	0 - o	5-24,1.165; 63-84,1.157; 96-127,1.144; 139-145,1.100; 46-52,1.097; 156-162,1.056	Asn_Glycosylation 40-43, 58-61; Ck2_Phospho_Site 46-49, 107-110; Myristyl 137-142, 159-164; Pkc_Phospho_Site 169-171; Lamp_1 61-75;	Lysosome-associated membrane glycoprotein (Lamp)/CD68

DEX0443_02 3.aa.3	Y	0 - o	5-24,1.165; 58-87,1.147; 46-52,1.097	Asn_Glycosylation 40-43, 58-61; Ck2_Phospho_Site 46-49; Myristyl 75-80;	
DEX0443_02 3.aa.4	N	1 - o236-258i	235-261,1.187; 165-177,1.167; 5-24,1.165; 196-228,1.160; 63-84,1.157; 138-147,1.152; 96-124,1.126; 46-52,1.097; 179-193,1.083; 154-160,1.064	Asn_Glycosylation 40-43, 58-61, 132-135; Ck2_Phospho_Site 46-49, 107-110; Myristyl 247-252; Pkc_Phospho_Site 140-142, 153-155; Lamp_1 61-75;	Lysosome-associated membrane glycoprotein (Lamp)/CD68
DEX0443_02 3.aa.6	N	1 - o277-299i	276-302,1.187; 206-218,1.167; 5-24,1.165; 237-269,1.160; 63-84,1.157; 179-188,1.152; 96-127,1.144; 139-145,1.100; 46-52,1.097; 220-234,1.083; 195-201,1.064	Asn_Glycosylation 40-43, 58-61, 173-176; Camp_Phospho_Site 162-165; Ck2_Phospho_Site 46-49, 107-110; Myristyl 137-142, 288-293; Pkc_Phospho_Site 181-183, 194-196; Lamp_1 61-75;	Lysosome-associated membrane glycoprotein (Lamp)/CD68
DEX0443_02 3.aa.7	N	1 - o329-351i	4-32,1.238; 328-354,1.187; 258-270,1.167; 289-321,1.160; 156-177,1.157; 38-61,1.154; 231-240,1.152; 73-122,1.145; 189-217,1.126; 139-145,1.097; 272-286,1.083; 247-253,1.064	Amidation 56-59; Asn_Glycosylation 151-154, 225-228; Ck2_Phospho_Site 139-142, 200-203; Myristyl 37-42, 39-44, 88-93, 340-345; Pkc_Phospho_Site 7-9, 18-20, 233-235, 246-248; Lamp_1 154-168;	Lysosome-associated membrane glycoprotein (Lamp)/CD68
DEX0443_02 5.aa.1	Y	0 - o	351-360,1.285; 4-15,1.269; 101-117,1.189; 150-164,1.148; 300-310,1.144; 264-294,1.134; 19-35,1.134; 184-200,1.124; 332-340,1.123; 207-220,1.112; 245-253,1.109; 312-319,1.085; 67-73,1.074; 119-138,1.065; 90-96,1.060; 238-243,1.051; 38-45,1.048; 229-235,1.042; 174-179,1.036	Asp_Protease 98-109; Asn_Glycosylation 95-98; Ck2_Phospho_Site 70-73, 173-176, 180-183, 226-229, 302-305, 331-334, 345-348, 353-356; Myristyl 137-142, 147-152, 151-156, 167-172, 230-235; Pkc_Phospho_Site 36-38, 70-72, 277-279, 353-355, 365-367; Crystallin_Betagamma 238-253; Prokar_Lipoprotein 268-278;	Crystallin; Pepsin (A1) aspartic protease; Eukaryotic and viral aspartic protease active site
DEX0443_02 6.aa.3	Y	4 - i7-29o44-61i81-98o113-135i	10-59,1.254; 111-139,1.227; 80-104,1.210; 235-243,1.169; 212-228,1.151; 246-265,1.150; 267-275,1.083; 162-168,1.063; 174-180,1.045	Asn_Glycosylation 200-203; Glycosaminoglycan 149-152; Myristyl 86-91, 96-101, 123-128, 128-133, 226-231, 233-238; Pkc_Phospho_Site 72-74, 172-174;	Cation efflux family; NULL

DEX0443_027.aa.1	N	0 - o	4-16,1.200; 118-136,1.135; 53-70,1.121; 84-100,1.118; 76-82,1.087; 163-172,1.086; 105-111,1.072; 18-35,1.070	Thioredoxin 91-109; Ck2_Phospho_Site 157-160, 166-169; Myristyl 16-21, 27-32, 42-47, 53-58; Pkc_Phospho_Site 37-39, 43-45, 148-150;	Thioredoxin
DEX0443_028.aa.1	N	0 - o	4-23,1.166; 53-62,1.137; 25-32,1.076	Camp_Phospho_Site 36-39; Myristyl 71-76;	
DEX0443_028.aa.3	N	0 - o	119-149,1.197; 32-87,1.174; 17-23,1.109; 89-95,1.106; 4-11,1.100; 104-110,1.031	Amidation 121-124; Glycosaminoglycan 15-18; Myristyl 16-21, 62-67, 93-98, 96-101, 114-119; Pkc_Phospho_Site 37-39; Prokar_Lipoprotein 73-83;	
DEX0443_030.aa.1	N	0 - i	9-21,1.314; 25-39,1.158	Ck2_Phospho_Site 40-43; Pkc_Phospho_Site 3-5;	
DEX0443_030.aa.2	N	1 - o15-37i	163-194,1.164; 148-161,1.149; 97-111,1.142; 69-86,1.136; 129-145,1.136; 34-54,1.104; 13-26,1.100	Ck2_Phospho_Site 87-90, 116-119, 148-151; Myristyl 142-147, 191-196; Pkc_Phospho_Site 45-47;	Binding-protein-dependent transport systems inner membrane component; MAPEG (Membrane-associated proteins in eicosanoid and glutathione metabolism); NULL
DEX0443_030.aa.3	N	1 - i55-77o	109-126,1.136; 137-143,1.135; 9-16,1.114; 74-94,1.104; 53-66,1.100; 41-47,1.090; 24-36,1.061	Ck2_Phospho_Site 41-44, 127-130; Pkc_Phospho_Site 23-25, 85-87;	NULL
DEX0443_030.aa.4	N	1 - i55-77o	171-179,1.124; 9-16,1.114; 74-94,1.104; 148-154,1.101; 53-66,1.100; 41-47,1.090; 126-134,1.087; 24-36,1.061	Asn_Glycosylation 137-140; Ck2_Phospho_Site 41-44, 139-142; Myristyl 171-176; Pkc_Phospho_Site 23-25, 85-87, 161-163, 164-166;	NULL
DEX0443_030.aa.5	N	0 - o	4-87,1.251; 104-112,1.142; 96-102,1.056	Pkc_Phospho_Site 41-43;	Immunoglobulin and major histocompatibility complex domain
DEX0443_030.aa.6	N	1 - i55-77o	118-145,1.168; 9-16,1.114; 74-94,1.104; 53-66,1.100; 41-47,1.090; 109-115,1.089; 24-36,1.061	Ck2_Phospho_Site 41-44; Pkc_Phospho_Site 23-25, 85-87;	NULL
DEX0443_030.aa.7	N	1 - i55-77o	9-16,1.114; 53-66,1.100; 41-47,1.090; 24-36,1.061; 74-80,1.059	Ck2_Phospho_Site 41-44; Pkc_Phospho_Site 23-25, 85-87;	
DEX0443_030.aa.8	N	0 - o	60-111,1.149; 41-57,1.136; 9-16,1.114; 24-37,1.082	Ck2_Phospho_Site 60-63; Myristyl 54-59, 103-108; Pkc Phospho Site	MAPEG (Membrane-associated proteins in eicosanoid and glutathione

				23-25;	metabolism); NULL
DEX0443_030.aa.9	y	0 - o	20-44,1.247; 91-142,1.149; 72-88,1.136; 10-17,1.098; 59-65,1.060	Ck2_Phospho_Site 91-94; Myristyl 26-31, 85-90, 134-139;	MAPEG (Membrane-associated proteins in eicosanoid and glutathione metabolism); NULL
DEX0443_032.aa.2	N	1 - i38-60o	331-347,1.304; 38-70,1.234; 108-123,1.200; 470-502,1.191; 355-365,1.166; 504-520,1.149; 253-271,1.143; 77-100,1.134; 160-177,1.121; 219-235,1.118; 461-468,1.117; 298-308,1.100; 211-217,1.087; 314-320,1.087; 19-33,1.079; 442-448,1.077; 240-246,1.072; 125-142,1.070; 408-414,1.067; 198-204,1.052; 434-440,1.032	Thioredoxin 91-109, 226-244; Ck2_Phospho_Site 66-69, 67-70, 202-205, 292-295, 301-304, 334-337, 359-362, 387-390, 419-422, 449-452; Myristyl 20-25, 51-56, 63-68, 123-128, 134-139, 149-154, 160-165, 184-189, 188-193, 445-450, 466-471, 498-503, 502-507; Pkc_Phospho_Site 37-39, 144-146, 150-152, 192-194, 201-203, 202-204, 283-285, 508-510; Prokar_Lipoprotein 45-55;	Thioredoxin
DEX0443_033.aa.1	N	0 - o	9-21,1.183; 162-173,1.135; 135-147,1.124; 333-358,1.121; 307-315,1.097; 68-80,1.085; 196-208,1.074; 82-104,1.070; 319-325,1.056		RNA-binding protein C2H2 Zn-finger domain; WW / rsp5 / WWP domain; U1-like zinc finger
DEX0443_033.aa.2	N	0 - o	356-398,1.245; 423-436,1.239; 26-43,1.189; 131-145,1.184; 589-599,1.174; 45-56,1.173; 210-228,1.167; 492-538,1.161; 438-455,1.150; 540-559,1.135; 237-249,1.127; 82-90,1.126; 282-289,1.113; 465-474,1.113; 4-17,1.107; 328-338,1.106; 268-280,1.098; 340-347,1.087; 412-421,1.071; 481-489,1.069; 63-71,1.063; 312-318,1.061; 153-159,1.060; 603-608,1.050	Amidation 181-184; Asn_Glycosylation 198-201, 329-332, 417-420, 522-525; Camp_Phospho_Site 576-579; Ck2_Phospho_Site 69-72, 93-96, 131-134, 132-135, 172-175, 236-239, 311-314, 410-413; Myristyl 341-346, 344-349, 353-358, 497-502, 555-560; Pkc_Phospho_Site 200-202, 236-238, 326-328, 331-333, 422-424, 437-439, 468-470, 493-495, 543-545, 587-589; Tyr_Phospho_Site 259-266; Ets_Domain_1 215-223; Ets_Domain_2 261-276;	Ets-domain; HSF/ETS DNA-binding domain; NULL
DEX0443_033.aa.3	y	0 - o	96-115,1.189; 145-161,1.189;	Amidation 62-65;	

			28-44,1.177; 9-18,1.140; 51-57,1.103; 63-71,1.086; 117-127,1.085	Ck2_Phospho_Site 147-150; Myristyl 35-40, 39-44, 72-77, 159-164; Pkc_Phospho_Site 25-27, 62-64;	
DEX0443_03 4.aa.2	N	0 - o	44-68,1.254; 140-149,1.164; 327-336,1.136; 353-358,1.128; 70-78,1.121; 5-11,1.110; 228-246,1.106; 164-172,1.079; 206-212,1.074; 24-30,1.067; 295-301,1.064; 274-283,1.059; 118-124,1.053; 261-267,1.047; 184-189,1.046; 155-160,1.034	Amidation 153-156; Asn_Glycosylation 327-330, 345-348; Ck2_Phospho_Site 92-95, 124-127, 175-178, 215-218, 277-280; Myristyl 19-24, 22-27, 31-36, 288-293, 289-294, 349-354; Pkc_Phospho_Site 26-28, 277-279;	NULL
DEX0443_03 5.aa.1	N	0 - o	92-109,1.185; 64-77,1.158; 23-36,1.141; 42-56,1.134	Asn_Glycosylation 60-63, 94-97; Ck2_Phospho_Site 42-45; Glycosaminoglycan 62-65, 90-93; Myristyl 112-117; Pkc_Phospho_Site 22-24;	
DEX0443_03 6.aa.1	y	0 - o	29-48,1.173; 55-75,1.114; 18-27,1.048	Amidation 16-19; Myristyl 7-12, 21-26, 24-29, 60-65; Pkc_Phospho_Site 64-66;	
DEX0443_03 7.aa.1	N	0 - o	72-89,1.221; 16-35,1.132; 43-63,1.080	Asn_Glycosylation 32-35, 59-62; Pkc_Phospho_Site 12-14;	
DEX0443_03 7.aa.2	y	1 - i22-44o	19-46,1.260; 140-149,1.160; 54-73,1.132; 5-12,1.131; 81-101,1.080; 161-171,1.056; 151-157,1.051; 123-135,1.041	Amidation 178-181; Asn_Glycosylation 70-73, 97-100; Ck2_Phospho_Site 7-10, 161-164; Pkc_Phospho_Site 50-52, 150-152; Tyr_Phospho_Site 152-158;	NULL
DEX0443_03 7.aa.3	y	1 - i22-44o	19-46,1.260; 169-185,1.221; 148-157,1.160; 131-144,1.136; 54-73,1.132; 5-12,1.131; 81-101,1.080; 113-128,1.071; 159-165,1.051	Asn_Glycosylation 70-73, 97-100; Ck2_Phospho_Site 7-10, 169-172; Pkc_Phospho_Site 50-52, 158-160; Tyr_Phospho_Site 160-166;	NULL
DEX0443_03 7.aa.4	N	0 - o	78-105,1.202; 35-44,1.070	Amidation 18-21, 26-29; Myristyl 41-46, 48-53, 49-54, 55-60, 62-67, 69-74, 74-79, 83-88; Pkc_Phospho_Site 18-20, 103-105;	NULL
DEX0443_03 9.aa.2	N	0 - o	38-51,1.199; 4-10,1.169;	Ck2_Phospho_Site 64-67, 213-216,	

			23-33,1.156; 131-140,1.101; 171-180,1.098; 204-219,1.095; 152-162,1.088; 182-197,1.081; 111-118,1.062	225-228; Myristyl 23-28, 24-29, 27-32, 56-61, 60-65; Pkc_Phospho_Site 31-33, 37-39, 61-63, 100-102, 150-152; Tyr_Phospho_Site 151-159, 152-159;	
DEX0443_039.aa.3	N	0 - o	21-36,1.095	Ck2_Phospho_Site 30-33, 42-45;	
DEX0443_039.aa.4	N	0 - o	30-55,1.226; 169-190,1.183; 124-149,1.183; 11-25,1.145; 84-92,1.128; 61-82,1.107; 99-106,1.075; 152-165,1.075; 115-120,1.042	Asn_Glycosylation 23-26, 45-48; Ck2_Phospho_Site 31-34, 158-161, 196-199; Myristyl 80-85, 115-120, 124-129, 128-133, 173-178; Pkc_Phospho_Site 168-170;	
DEX0443_041.aa.8	N	0 - o	4-10,1.234; 65-74,1.192; 12-44,1.117; 51-60,1.101; 80-88,1.081	Amidation 79-82; Asn_Glycosylation 26-29; Ck2_Phospho_Site 44-47; Myristyl 13-18, 83-88; Pkc_Phospho_Site 28-30;	Rhodanese/cdc25 fold
DEX0443_041.aa.11	N	0 - o	129-138,1.192; 24-44,1.189; 51-62,1.170; 4-17,1.152; 64-71,1.141; 86-97,1.108; 115-124,1.101; 144-152,1.081; 102-108,1.060	Amidation 143-146; Ck2_Phospho_Site 66-69, 108-111; Myristyl 33-38, 147-152; Pkc_Phospho_Site 23-25, 59-61;	Rhodanese/cdc25 fold
DEX0443_041.aa.12	Y	2 - i12-31o239-261i	320-332,1.259; 121-140,1.247; 233-260,1.240; 4-39,1.236; 296-317,1.216; 45-55,1.173; 276-285,1.160; 195-204,1.131; 147-154,1.129; 70-77,1.128; 287-294,1.100; 185-192,1.094; 106-112,1.087; 84-93,1.069	Asn_Glycosylation 190-193; Ck2_Phospho_Site 39-42, 87-90, 105-108, 123-126, 157-160, 159-162, 198-201, 208-211, 299-302; Myristyl 110-115, 121-126, 163-168, 224-229, 242-247, 261-266, 294-299, 314-319; Pkc_Phospho_Site 62-64, 74-76, 100-102, 184-186, 274-276, 321-323;	Immunoglobulin and major histocompatibility complex domain; Immunoglobulin V-type; Immunoglobulin C-2 type; Immunoglobulin subtype
DEX0443_041.aa.13	Y	3 - i12-31o76-98i290-312o	173-192,1.247; 285-312,1.240; 4-39,1.236; 68-107,1.236; 53-62,1.136; 247-256,1.131; 199-206,1.129; 122-129,1.128; 327-336,1.114; 237-244,1.094; 158-164,1.087; 136-145,1.069	Asn_Glycosylation 242-245; Camp_Phospho_Site 327-330; Ck2_Phospho_Site 39-42, 139-142, 157-160, 175-178, 209-212, 211-214, 250-253, 260-263, 344-347; Myristyl 54-59, 58-63, 162-167,	Immunoglobulin and major histocompatibility complex domain; Immunoglobulin V-type; Immunoglobulin C-2 type; Immunoglobulin subtype

				173-178, 215-220, 276-281, 294-299, 313-318; Pkc_Phospho_Site 63-65, 114-116, 126-128, 152-154, 236-238, 326-328, 331-333, 332-334, 341-343;	
DEX0443_04 1.aa.14	Y	0 - o	89-110,1.236; 60-86,1.225; 140-151,1.160; 154-180,1.149; 7-32,1.128; 196-203,1.118; 211-223,1.090; 51-58,1.073; 229-235,1.035	Amidation 209-212; Myristyl 14-19, 192-197; Pkc_Phospho_Site 37-39, 65-67; Prokar_Lipoprotein 172-182;	
DEX0443_04 1.aa.2	N	0 - o	29-38,1.192; 15-24,1.101; 44-52,1.081	Amidation 43-46; Ck2_Phospho_Site 5-8; Myristyl 47-52;	
DEX0443_04 1.aa.3	N	0 - o	35-59,1.135; 83-96,1.112; 15-23,1.103; 66-74,1.096	Ck2_Phospho_Site 99-102; Myristyl 19-24, 90-95, 96-101; Pkc_Phospho_Site 39-41, 44-46, 66-68, 75-77;	
DEX0443_04 1.aa.4	N	0 - o	177-186,1.192; 24-44,1.189; 51-62,1.170; 4-17,1.152; 64-71,1.141; 86-97,1.108; 103-126,1.107; 163-172,1.101; 140-156,1.100; 192-200,1.081	Amidation 191-194; Ck2_Phospho_Site 66-69, 118-121, 138-141, 156-159; Myristyl 33-38, 145-150, 195-200; Pkc_Phospho_Site 23-25, 59-61, 128-130;	Rhodanese/cdc25 fold
DEX0443_04 1.aa.5	N	0 - o	156-165,1.192; 24-44,1.189; 51-62,1.170; 4-17,1.152; 64-71,1.141; 86-97,1.108; 142-151,1.101; 119-135,1.100; 171-179,1.081	Amidation 170-173; Ck2_Phospho_Site 66-69, 117-120, 135-138; Myristyl 33-38, 106-111, 124-129, 174-179; Pkc_Phospho_Site 23-25, 59-61;	Rhodanese/cdc25 fold
DEX0443_04 1.aa.6	N	0 - o	62-71,1.192; 48-57,1.101; 25-41,1.100; 77-85,1.081	Amidation 76-79; Ck2_Phospho_Site 23-26, 41-44; Myristyl 30-35, 80-85;	Rhodanese/cdc25 fold
DEX0443_04 1.aa.7	N	0 - o	88-97,1.192; 4-37,1.107; 74-83,1.101; 51-67,1.100; 103-111,1.081	Amidation 102-105; Ck2_Phospho_Site 29-32, 49-52, 67-70; Myristyl 56-61, 106-111; Pkc_Phospho_Site 9-11, 39-41;	Rhodanese/cdc25 fold
DEX0443_04 2.aa.1	N	3 - i13-35o50-72i100-122o	12-42,1.290; 49-61,1.272; 99-129,1.187; 79-85,1.072; 68-74,1.055; 87-95,1.041	Myristyl 65-70, 115-120; Prokar_Lipoprotein 119-129;	MIP family
DEX0443_04	Y	2 - i2-	4-22,1.290;	Myristyl 45-50;	MIP family

2.aa.2		19o29-51i	29-41,1.272; 59-65,1.072; 48-54,1.055; 67-73,1.035		
DEX0443_04 2.aa.3	N	6 - i54-76o86-108i129 - 151o232 - 254i267 - 289o317 -336i	242-260,1.290; 267-279,1.272; 44-78,1.213; 317-347,1.187; 126-171,1.159; 356-364,1.149; 86-124,1.139; 4-29,1.106; 33-42,1.102; 207-214,1.098; 190-199,1.079; 297-303,1.072; 220-228,1.065; 286-292,1.055; 182-187,1.042; 305-313,1.041	Asn_Glycosylation 221-224; Ck2_Phospho_Site 355-358; Myristyl 84-89, 87-92, 103-108, 108-113, 144-149, 150-155, 154-159, 225-230, 283-288, 333-338; Mip 114-122; Prokar_Lipoprotein 63-73, 337-347;	MIP family
DEX0443_04 2.aa.4	Y	3 - o79-101i114 - 136o164 -183i	89-107,1.290; 114-126,1.272; 164-194,1.187; 4-16,1.173; 203-211,1.149; 31-51,1.136; 54-61,1.098; 144-150,1.072; 67-75,1.065; 133-139,1.055; 152-160,1.041	Asn_Glycosylation 68-71; Ck2_Phospho_Site 202-205; Myristyl 72-77, 130-135, 180-185; Prokar_Lipoprotein 184-194;	MIP family
DEX0443_04 3.aa.1	N	0 - o	13-24,1.138; 80-102,1.114	S100_Cabp 68-89; Asn_Glycosylation 36-39; Ck2_Phospho_Site 11-14, 13-16, 40-43, 74-77; Myristyl 91-96; Pkc_Phospho_Site 15-17, 106-108; Ef_Hand 73-85; Prokar_Lipoprotein 86-96;	S-100/ICaBP type calcium binding protein; EF-hand
DEX0443_04 4.aa.1	N	0 - o	71-91,1.147; 100-110,1.136; 27-39,1.129; 131-153,1.127; 61-69,1.119; 199-206,1.110; 112-121,1.100; 159-174,1.094; 210-219,1.086; 41-54,1.068; 11-19,1.058	Asn_Glycosylation 14-17; Ck2_Phospho_Site 55-58, 94-97, 181-184, 200-203, 219-222; Myristyl 28-33, 146-151, 178-183; Pkc_Phospho_Site 219-221;	
DEX0443_04 4.aa.2	N	0 - o	169-184,1.231; 68-83,1.184; 200-219,1.173; 140-159,1.148; 28-66,1.147; 299-319,1.147; 5-20,1.136; 328-338,1.136; 255-267,1.129; 359-381,1.127; 289-297,1.119; 427-434,1.110; 221-229,1.103; 340-349,1.100; 190-198,1.098; 117-126,1.095; 387-402,1.094; 438-447,1.086; 269-282,1.062; 239-247,1.058;	Rnp_1 174-181; Asn_Glycosylation 96-99, 242-245; Camp_Phospho_Site 114-117; Ck2_Phospho_Site 69-72, 98-101, 126-129, 283-286, 322-325, 409-412, 428-431, 447-450; Myristyl 12-17, 21-26, 91-96, 122-127, 160-165, 256-261, 374-379, 406-411; Pkc_Phospho_Site 447-449;	RNA-binding region RNP-1 (RNA recognition motif); Aminopeptidase N, APN (CD13)

			101-106,1.048		
DEX0443_04 4.aa.3	N	0 - o	85-100,1.231; 116-135,1.173; 62-75,1.153; 215-235,1.147; 244-254,1.136; 6-32,1.130; 171-183,1.129; 275-297,1.127; 205-213,1.119; 343-350,1.110; 137-145,1.103; 256-265,1.100; 106-114,1.098; 303-318,1.094; 37-54,1.090; 354-363,1.086; 185-198,1.062; 155-163,1.058	Rnp_1 90-97; Asn_Glycosylation 158-161; Ck2_Phospho_Site 199-202, 238-241, 325-328, 344-347, 363-366; Myristyl 71-76, 76-81, 172-177, 290-295, 322-327; Pkc_Phospho_Site 20-22, 27-29, 363-365;	RNA-binding region RNP-1 (RNA recognition motif)
DEX0443_04 4.aa.4	N	0 - o	355-370,1.231; 155-177,1.222; 416-488,1.204; 40-53,1.194; 96-144,1.189; 254-269,1.184; 506-525,1.173; 326-345,1.148; 225-252,1.147; 605-625,1.147; 189-219,1.145; 57-80,1.139; 634-644,1.136; 376-406,1.135; 561-573,1.129; 4-36,1.128; 665-687,1.127; 595-603,1.119; 733-740,1.110; 527-535,1.103; 646-655,1.100; 303-312,1.095; 693-708,1.094; 491-504,1.094; 744-753,1.086; 575-588,1.062; 545-553,1.058; 287-292,1.048	Rnp_1 360-367; Asn_Glycosylation 118-121, 282-285, 548-551; Camp_Phospho_Site 300-303; Ck2_Phospho_Site 86-89, 216-219, 255-258, 284-287, 312-315, 589-592, 628-631, 715-718, 734-737, 753-756; Myristyl 5-10, 43-48, 62-67, 277-282, 308-313, 346-351, 411-416, 415-420, 473-478, 562-567, 680-685, 712-717; Pkc_Phospho_Site 204-206, 416-418, 753-755;	RNA-binding region RNP-1 (RNA recognition motif); Proline-rich region; Aminopeptidase N, APN (CD13)
DEX0443_04 5.aa.1	N	0 - o	15-27,1.138		
DEX0443_04 6.aa.2	N	0 - o	155-180,1.130; 19-35,1.124; 101-118,1.114; 129-153,1.114; 42-55,1.112; 192-217,1.110; 80-88,1.109; 90-98,1.086; 182-190,1.072; 73-78,1.051; 64-70,1.042	Asp_Protease 118-129; Ck2_Phospho_Site 11-14, 61-64, 180-183, 220-223; Myristyl 65-70, 169-174, 187-192, 230-235; Pkc_Phospho_Site 131-133; Crystallin_Betagamma 73-88;	Crystallin; Pepsin (A1) aspartic protease; Eukaryotic and viral aspartic protease active site
DEX0443_04 7.aa.2	N	0 - i	8-26,1.184	Amidation 36-39; Asn_Glycosylation 32-35; Camp_Phospho_Site 38-41; Pkc_Phospho_Site 31-33, 34-36, 41-43;	
DEX0443_04 9.aa.1	N	0 - o	72-88,1.205; 143-151,1.196; 29-64,1.191; 224-270,1.182;	Tnfr_Ngfr_1 26-63, 66-107; Asn_Glycosylation 23-26, 160-	Proline-rich region; TNFR/CD27/30/40/95 cysteine-rich region; NULL

			101-129,1.143; 159-167,1.132; 4-14,1.131; 302-314,1.094; 90-96,1.092; 189-195,1.087; 171-178,1.080; 280-285,1.067; 317-331,1.060; 338-344,1.040; 201-206,1.036; 214-219,1.034	163; Camp_Phospho_Site 102-105; Ck2_Phospho_Site 25-28, 65-68, 70-73, 123-126, 135-138, 172-175, 270-273; Myristyl 3-8, 48-53, 112-117, 146-151, 178-183, 185-190, 294-299, 299-304; Pkc_Phospho_Site 25-27, 52-54, 100-102, 101-103, 192-194; Tyr_Phospho_Site 27-33;	
DEX0443_04 9.aa.2	Y	0 - o	94-110,1.205; 165-173,1.196; 51-86,1.191; 246-292,1.182; 123-151,1.170; 9-36,1.166; 182-189,1.113; 324-336,1.094; 112-118,1.092; 211-217,1.087; 193-200,1.080; 302-307,1.067; 378-385,1.063; 339-353,1.060; 360-366,1.040; 223-228,1.036; 236-241,1.034	Tnfr_Ngfr_1 48-85, 88-129; Asn_Glycosylation 45-48, 182-185; Camp_Phospho_Site 124-127; Ck2_Phospho_Site 47-50, 87-90, 92-95, 145-148, 157-160, 194-197, 292-295; Myristyl 28-33, 70-75, 134-139, 168-173, 200-205, 207-212, 316-321, 321-326, 388-393; Pkc_Phospho_Site 47-49, 74-76, 122-124, 123-125, 187-189, 214-216, 392-394; Tyr_Phospho_Site 49-55;	Proline-rich region; TNFR/CD27/30/40/95 cysteine-rich region; NULL
DEX0443_04 9.aa.3	Y	1 - o226-248i	227-264,1.216; 94-110,1.205; 165-173,1.196; 51-86,1.191; 282-328,1.182; 123-151,1.170; 9-36,1.166; 182-189,1.113; 360-372,1.094; 112-118,1.092; 211-217,1.087; 193-200,1.080; 338-343,1.067; 414-421,1.063; 375-389,1.060; 396-402,1.040; 272-277,1.034	Tnfr_Ngfr_1 48-85, 88-129; Asn_Glycosylation 45-48, 182-185; Camp_Phospho_Site 124-127; Ck2_Phospho_Site 47-50, 87-90, 92-95, 145-148, 157-160, 194-197, 328-331; Myristyl 28-33; 70-75, 134-139, 168-173, 200-205, 207-212, 352-357, 357-362, 424-429; Pkc_Phospho_Site 47-49, 74-76, 122-124, 123-125, 187-189, 214-216, 428-430; Tyr_Phospho_Site 49-55; Prokar_Lipoprotein 241-251;	Proline-rich region; TNFR/CD27/30/40/95 cysteine-rich region; NULL
DEX0443_04	y	1 -	227-264,1.216;	Tnfr_Ngfr_1 48-	Proline-rich region;

9.aa.4		o226-248i	94-110,1.205; 424-442,1.202; 165-173,1.196; 51-86,1.191; 282-328,1.182; 123-151,1.170; 9-36,1.166; 182-189,1.113; 360-372,1.094; 112-118,1.092; 211-217,1.087; 193-200,1.080; 338-343,1.067; 414-421,1.063; 375-389,1.060; 396-402,1.040; 272-277,1.034	85, 88-129; Asn_Glycosylation 45-48, 182-185; Camp_Phospho_Site 124-127; Ck2_Phospho_Site 47-50, 87-90, 92-95, 145-148, 157-160, 194-197, 328-331, 448-451, 450-453; Myristyl 28-33, 70-75, 134-139, 168-173, 200-205, 207-212, 352-357, 357-362, 424-429; Pkc_Phospho_Site 47-49, 74-76, 122-124, 123-125, 187-189, 214-216; Tyr_Phospho_Site 49-55; Prokar_Lipoprotein 241-251;	TNFR/CD27/30/40/95 cysteine-rich region; NULL
DEX0443_04 9.aa.5	y	1 - o426-448i	344-423,1.224; 427-464,1.216; 94-110,1.205; 165-173,1.196; 296-325,1.193; 51-86,1.191; 482-528,1.182; 268-294,1.175; 123-151,1.170; 9-36,1.166; 224-241,1.144; 247-265,1.134; 182-189,1.113; 560-572,1.094; 112-118,1.092; 211-217,1.087; 193-200,1.080; 538-543,1.067; 614-621,1.063; 575-589,1.060; 596-602,1.040; 472-477,1.034	Tnfr_Ngfr_1 48-85, 88-129; Amidation 387-390; Asn_Glycosylation 45-48, 182-185; Camp_Phospho_Site 124-127; Ck2_Phospho_Site 47-50, 87-90, 92-95, 145-148, 157-160, 194-197, 528-531; Myristyl 28-33, 70-75, 134-139, 168-173, 200-205, 207-212, 248-253, 291-296, 381-386, 401-406, 416-421, 552-557, 557-562, 624-629; Pkc_Phospho_Site 47-49, 74-76, 122-124, 123-125, 187-189, 214-216, 326-328, 336-338, 628-630; Tyr_Phospho_Site 49-55; Prokar_Lipoprotein 441-451;	Proline-rich region; TNFR/CD27/30/40/95 cysteine-rich region; NULL
DEX0443_04 9.aa.6	y	0 - o	13-25,1.182; 41-87,1.182; 119-131,1.094; 97-102,1.067; 173-180,1.063; 134-148,1.060; 155-161,1.040; 31-36,1.034	Camp_Phospho_Site 14-17; Ck2_Phospho_Site 87-90; Myristyl 111-116, 116-121, 183-188; Pkc_Phospho_Site 187-189;	Proline-rich region
DEX0443_04 9.aa.7	y	1 - o226-248i	227-265,1.216; 94-110,1.205; 165-173,1.196; 51-86,1.191;	Tnfr_Ngfr_1 48-85, 88-129; Asn_Glycosylation 45-48, 182-	TNFR/CD27/30/40/95 cysteine-rich region; NULL

			123-151,1.170; 9-36,1.166; 182-189,1.113; 112-118,1.092; 211-217,1.087; 193-200,1.080	185; Camp_Phospho_Site 124-127; Ck2_Phospho_Site 47-50, 87-90, 92-95, 145-148, 157-160, 194-197, 293-296; Myristyl 28-33, 70-75, 134-139, 168-173, 200-205, 207-212, 276-281, 289-294; Pkc_Phospho_Site 47-49, 74-76, 122-124, 123-125, 187-189, 214-216; Rgd 285-287; Tyr_Phospho_Site 49-55; Prokar_Lipoprotein 241-251;	
DEX0443_051.aa.3	N	1 - o1076-1098i	75-97,1.213; 511-523,1.208; 101-127,1.205; 300-322,1.204; 830-853,1.199; 669-688,1.196; 785-803,1.189; 1067-1094,1.185; 391-399,1.184; 327-340,1.179; 1105-1124,1.175; 50-63,1.170; 757-776,1.166; 732-749,1.164; 183-214,1.156; 601-609,1.153; 159-167,1.149; 696-708,1.147; 257-270,1.146; 556-567,1.145; 488-500,1.135; 878-885,1.134; 624-642,1.127; 897-912,1.125; 1024-1031,1.115; 811-828,1.115; 441-455,1.113; 865-875,1.108; 292-298,1.101; 470-480,1.099; 584-599,1.097; 362-370,1.093; 1046-1054,1.091; 377-384,1.090; 138-143,1.090; 1096-1102,1.088; 942-948,1.087; 1015-1022,1.080; 346-352,1.078; 14-19,1.077; 413-423,1.077; 569-576,1.075; 229-238,1.074; 541-547,1.070; 919-925,1.063;	Asn_Glycosylation 689-692, 754-757; Ck2_Phospho_Site 9-12, 12-15, 42-45, 206-209, 303-306, 378-381, 392-395, 480-483, 624-627, 722-725, 784-787, 810-813, 934-937; Myristyl 232-237, 431-436, 503-508, 620-625, 758-763, 921-926, 944-949; Pkc_Phospho_Site 68-70, 224-226, 243-245, 347-349, 409-411, 435-437, 472-474, 572-574, 732-734, 997-999; Tyr_Phospho_Site 702-709; His_Acid_Phosphat_1 396-410;	Histidine acid phosphatase

			275-281,1.062; 984-990,1.061; 998-1004,1.059; 970-976,1.055; 650-656,1.047; 1034-1041,1.034; 658-665,1.032		
DEX0443_051.aa.4	Y	0 - 0	28-41,1.179; 4-23,1.161; 47-52,1.078	Pkc_Phospho_Site 48-50;	
DEX0443_051.aa.5	N	0 - 0	40-69,1.205; 6-12,1.070; 15-38,1.069	Ck2_Phospho_Site 5-8; Myristyl 54-59; Prokar_Lipoprotein 59-69;	
DEX0443_054.aa.1	N	0 - 0	41-70,1.189; 4-17,1.152; 19-32,1.139	Ck2_Phospho_Site 21-24, 61-64, 75-78; Myristyl 88-93; Pkc_Phospho_Site 54-56;	Ligand-binding domain of nuclear hormone receptor
DEX0443_055.aa.2	N	0 - 0	206-216,1.161; 224-270,1.139; 134-141,1.105; 155-161,1.069; 170-176,1.057; 189-197,1.056; 181-187,1.046	Camp_Phospho_Site 27-30, 43-46, 56-59, 96-99; Ck2_Phospho_Site 71-74, 82-85, 98-101, 99-102; Pkc_Phospho_Site 14-16, 22-24, 51-53, 71-73, 95-97, 135-137, 235-237;	NULL
DEX0443_055.aa.3	N	0 - 0	45-57,1.088; 131-139,1.087; 31-38,1.077; 82-99,1.054; 19-25,1.048; 121-127,1.043	Asn_Glycosylation 20-23, 30-33; Ck2_Phospho_Site 32-35, 65-68; Pkc_Phospho_Site 22-24, 32-34, 48-50, 142-144;	NULL
DEX0443_057.aa.2	N	0 - 0	53-85,1.167; 23-46,1.136; 13-21,1.113	Amidation 14-17; Pkc_Phospho_Site 3-5, 98-100;	
DEX0443_057.aa.3	N	0 - 0	16-29,1.174; 4-14,1.170; 54-62,1.151; 37-43,1.094; 69-74,1.058	Myristyl 34-39, 56-61, 57-62; Pkc_Phospho_Site 28-30; Rgd 69-71; Prokar_Lipoprotein 19-29, 54-64;	
DEX0443_057.aa.4	N	0 - 0	143-153,1.228; 53-85,1.167; 111-141,1.157; 23-46,1.136; 13-21,1.113; 94-109,1.111	Amidation 14-17; Myristyl 150-155; Pkc_Phospho_Site 3-5, 98-100, 125-127;	
DEX0443_058.aa.1	N	0 - 0	61-84,1.209; 28-40,1.130; 10-19,1.130; 97-116,1.105; 49-55,1.060	Camp_Phospho_Site 51-54; Ck2_Phospho_Site 13-16; Pkc_Phospho_Site 41-43, 56-58, 62-64; Tyr_Phospho_Site 5-12;	Ribosomal protein L1
DEX0443_058.aa.2	N	0 - 0	30-42,1.130; 11-20,1.130; 51-56,1.091	Camp_Phospho_Site 53-56; Ck2_Phospho_Site 14-17; Pkc_Phospho_Site 3-5, 43-45, 58-	

				60; Tyr_Phospho_Site 7-14;	
DEXO443_05 8.aa.3	N	0 - i	4-50,1.172; 60-75,1.115; 81-89,1.094	Myristyl 43-48; Pkc_Phospho_Site 28-30, 71-73;	
DEXO443_05 8.aa.4	N	0 - o	6-19,1.134; 42-49,1.111; 22-32,1.100	Ck2_Phospho_Site 23-26;	
DEXO443_05 9.aa.2	N	0 - o	66-78,1.231; 115-126,1.181; 152-171,1.170; 4-29,1.161; 328-335,1.156; 380-399,1.130; 52-62,1.129; 342-355,1.121; 181-194,1.117; 99-112,1.116; 133-150,1.101; 304-320,1.087	Atp_Gtp_A 223-230; Asn_Glycosylation 257-260, 268-271; Ck2_Phospho_Site 63-66, 93-96, 101-104, 113-116, 118-121, 177-180, 192-195, 247-250, 273-276, 293-296, 320-323, 375-378; Myristyl 28-33, 52-57, 106-111, 149-154, 182-187, 265-270, 302-307, 361-366; Pkc_Phospho_Site 32-34, 233-235, 244-246, 270-272, 375-377;	Proline-rich region; ATP/GTP-binding site motif A (P-loop)
DEXO443_05 9.aa.3	y	0 - o	201-235,1.223; 128-141,1.209; 5-21,1.185; 155-171,1.175; 33-54,1.174; 82-95,1.153; 60-66,1.125; 106-119,1.097; 181-194,1.090; 74-79,1.060	Camp_Phospho_Site 37-40; Ck2_Phospho_Site 101-104; Myristyl 127-132; Pkc_Phospho_Site 35-37, 52-54, 70-72, 183-185; Tyr_Phospho_Site 116-123; Polyprenyl_Synthet_1 172-186;	Polyprenyl synthetase
DEXO443_06 0.aa.2	N	0 - o	175-185,1.225; 124-165,1.203; 362-370,1.179; 25-49,1.169; 280-315,1.154; 73-90,1.133; 9-15,1.130; 111-121,1.127; 323-341,1.121; 95-102,1.121; 253-265,1.112; 201-211,1.092; 55-61,1.085; 350-357,1.074; 243-250,1.061; 269-278,1.061	Asn_Glycosylation 56-59, 349-352; Ck2_Phospho_Site 123-126, 174-177, 233-236, 235-238, 313-316, 323-326, 357-360; Myristyl 60-65, 229-234, 362-367; Pkc_Phospho_Site 73-75, 76-78, 301-303, 354-356, 363-365; Tyr_Phospho_Site 303-309;	
DEXO443_06 0.aa.3	N	0 - o	175-185,1.225; 124-165,1.203; 473-482,1.179; 25-49,1.169; 578-589,1.155; 280-315,1.154; 394-416,1.152; 368-384,1.143; 424-465,1.143; 489-499,1.139; 73-90,1.133;	Asn_Glycosylation 56-59; Ck2_Phospho_Site 123-126, 174-177, 233-236, 235-238, 313-316, 323-326, 545-548, 645-648, 658-661; Leucine_Zipper 458-479;	

			9-15,1.130; 111-121,1.127; 323-355,1.122; 95-102,1.121; 521-528,1.118; 253-265,1.112; 539-548,1.107; 601-618,1.106; 201-211,1.092; 623-630,1.089; 55-61,1.085; 655-665,1.082; 386-392,1.069; 557-564,1.066; 243-250,1.061; 269-278,1.061; 507-513,1.056; 633-639,1.052; 360-365,1.048	Myristyl 60-65, 229-234, 354-359, 366-371, 512-517; Pkc_Phospho_Site 73-75, 76-78, 301-303, 518-520, 531-533, 560-562, 593-595, 636-638, 637-639, 657-659; Tyr_Phospho_Site 303-309;	
DEX0443_060.aa.6	N	0 - o	4-25,1.169; 100-114,1.165; 49-66,1.133; 87-97,1.127; 71-78,1.121; 31-37,1.085	Asn_Glycosylation 32-35; Ck2_Phospho_Site 99-102; Myristyl 36-41; Pkc_Phospho_Site 49-51, 52-54;	
DEX0443_060.aa.7	N	0 - i	54-64,1.148; 42-50,1.103; 69-82,1.079; 28-33,1.073	Amidation 29-32; Camp_Phospho_Site 42-45; Myristyl 33-38, 83-88; Pkc_Phospho_Site 56-58, 68-70, 78-80;	
DEX0443_061.aa.2	N	0 - o	4-16,1.105; 24-38,1.103; 41-50,1.071	Glycosaminoglycan 59-62; Pkc_Phospho_Site 3-5, 53-55, 59-61;	
DEX0443_062.aa.1	N	0 - o	41-51,1.181; 148-157,1.148; 173-180,1.141; 58-74,1.121; 22-38,1.115; 4-19,1.099; 77-88,1.088; 103-115,1.072; 117-129,1.064; 92-101,1.058	Ubiquitin_1 34-59; Amidation 185-188; Camp_Phospho_Site 162-165; Ck2_Phospho_Site 25-28, 72-75; Glycosaminoglycan 107-110; Pkc_Phospho_Site 99-101, 118-120, 165-167;	Ubiquitin domain
DEX0443_062.aa.2	N	0 - o	52-59,1.141; 12-20,1.088; 24-32,1.042	Amidation 64-67; Camp_Phospho_Site 41-44; Pkc_Phospho_Site 31-33, 44-46;	
DEX0443_064.aa.1	Y	1 - o252-274i	251-283,1.275; 216-228,1.194; 180-192,1.149; 61-71,1.145; 6-32,1.142; 96-114,1.119; 172-178,1.104; 142-160,1.096; 38-43,1.087; 236-242,1.071; 79-84,1.064; 88-94,1.049	Tissue_Factor 82-99; Amidation 200-203; Asn_Glycosylation 48-51, 161-164, 174-177; Camp_Phospho_Site 237-240; Ck2_Phospho_Site 58-61, 90-93, 92-95, 125-128, 163-166, 179-182, 242-245, 290-293; Myristyl 36-41, 39-44, 118-123, 157-162, 248-	Cytokine receptor class 2 family; Tissue Factor (TF)

				253, 286-291; Pkc_Phospho_Site 50-52, 76-78, 179-181, 200-202, 204-206, 290-292;	
DEX0443_066.aa.1	N	0 - 0	9-21,1.183; 162-173,1.135; 135-147,1.124; 333-358,1.121; 307-315,1.097; 68-80,1.085; 196-208,1.074; 82-104,1.070; 319-325,1.056		RNA-binding protein C2H2 Zn-finger domain; WW / rsp5 / WWP domain; U1-like zinc finger
DEX0443_066.aa.2	N	0 - 0	356-398,1.245; 423-436,1.239; 26-43,1.189; 131-145,1.184; 589-599,1.174; 45-56,1.173; 210-228,1.167; 492-538,1.161; 438-455,1.150; 540-559,1.135; 237-249,1.127; 82-90,1.126; 282-289,1.113; 465-474,1.113; 4-17,1.107; 328-338,1.106; 268-280,1.098; 340-347,1.087; 412-421,1.071; 481-489,1.069; 63-71,1.063; 312-318,1.061; 153-159,1.060; 603-608,1.050	Amidation 181-184; Asn_Glycosylation 198-201, 329-332, 417-420, 522-525; Camp_Phospho_Site 576-579; Ck2_Phospho_Site 69-72, 93-96, 131-134, 132-135, 172-175, 236-239, 311-314, 410-413; Myristyl 341-346, 344-349, 353-358, 497-502, 555-560; Pkc_Phospho_Site 200-202, 236-238, 326-328, 331-333, 422-424, 437-439, 468-470, 493-495, 543-545, 587-589; Tyr_Phospho_Site 259-266; Ets_Domain_1 215-223; Ets_Domain_2 261-276;	Ets-domain; HSF/ETS DNA-binding domain; NULL
DEX0443_067.aa.1	N	0 - 0	4-11,1.149; 45-54,1.095; 29-34,1.048	Asn_Glycosylation 24-27; Camp_Phospho_Site 42-45; Ck2_Phospho_Site 26-29, 54-57; Myristyl 19-24, 50-55;	Aminopeptidase N, APN (CD13)
DEX0443_071.aa.1	N	0 - 0	41-51,1.181; 148-157,1.148; 173-180,1.141; 58-74,1.121; 22-38,1.115; 4-19,1.099; 77-88,1.088; 103-115,1.072; 117-129,1.064; 92-101,1.058	Ubiquitin_1 34-59; Amidation 185-188; Camp_Phospho_Site 162-165; Ck2_Phospho_Site 25-28, 72-75; Glycosaminoglycan 107-110; Pkc_Phospho_Site 99-101, 118-120, 165-167;	Ubiquitin domain
DEX0443_075.aa.1	N	0 - 0	23-35,1.178; 213-239,1.178; 140-168,1.155; 241-249,1.130; 290-299,1.123; 195-211,1.089; 279-285,1.080; 57-71,1.076;	Asn_Glycosylation 19-22, 46-49, 137-140; Ck2_Phospho_Site 77-80, 139-142, 239-242, 243-246; Myristyl 15-20, 44-49,	Lipocalin-related protein and Bos/Can/Equ allergen; Lipocalin

			100-106,1.070; 170-176,1.068; 79-89,1.060; 8-15,1.052; 261-266,1.025	68-73, 92-97, 97-102, 101-106, 115-120, 233-238; Pkc_Phospho_Site 74-76, 77-79, 119-121, 188-190, 212-214, 274-276, 303-305;	
DEX0443_076.aa.1	N	0 - i	21-29,1.168; 63-80,1.159; 103-111,1.144; 82-96,1.123; 148-157,1.113; 54-60,1.086; 135-143,1.070; 125-133,1.062	Amidation 9-12; Camp_Phospho_Site 13-16; Ck2_Phospho_Site 149-152; Myristyl 79-84, 88-93; Pkc_Phospho_Site 20-22, 59-61, 67-69, 74-76, 149-151; Ribosomal_L21e 43-68;	Ribosomal protein L21E
DEX0443_077.aa.1	N	0 - o	72-88,1.205; 143-151,1.196; 29-64,1.191; 224-270,1.182; 101-129,1.143; 159-167,1.132; 4-14,1.131; 302-314,1.094; 90-96,1.092; 189-195,1.087; 171-178,1.080; 280-285,1.067; 317-331,1.060; 338-344,1.040; 201-206,1.036; 214-219,1.034	Tnfr_Ngfr_1 26-63, 66-107; Asn_Glycosylation 23-26, 160-163; Camp_Phospho_Site 102-105; Ck2_Phospho_Site 25-28, 65-68, 70-73, 123-126, 135-138, 172-175, 270-273; Myristyl 3-8, 48-53, 112-117, 146-151, 178-183, 185-190, 294-299, 299-304; Pkc_Phospho_Site 25-27, 52-54, 100-102, 101-103, 192-194; Tyr_Phospho_Site 27-33;	Proline-rich region; TNFR/CD27/30/40/95 cysteine-rich region; NULL
DEX0443_081.aa.1	N	0 - o	13-24,1.138; 80-102,1.114	S100_Cabp 68-89; Asn_Glycosylation 36-39; Ck2_Phospho_Site 11-14, 13-16, 40-43, 74-77; Myristyl 91-96; Pkc_Phospho_Site 15-17, 106-108; Ef_Hand 73-85; Prokar_Lipoprotein 86-96;	S-100/ICaBP type calcium binding protein; EF-hand
DEX0443_093.aa.1	N	0 - o	50-67,1.164; 35-48,1.140; 4-12,1.093; 16-22,1.087	Ck2_Phospho_Site 15-18;	
DEX0443_094.aa.1	N	0 - o	71-83,1.182; 90-97,1.134; 211-219,1.127; 130-141,1.117; 186-193,1.076; 59-65,1.067; 195-202,1.065; 226-240,1.059; 169-177,1.041	Asn_Glycosylation 13-16, 40-43; Ck2_Phospho_Site 119-122, 125-128, 149-152, 162-165, 214-217, 225-228; Myristyl 134-139; Pkc_Phospho_Site 105-107, 173-	Osteopontin; NULL

				175; Rgd 93-95; Tyr_Phospho_Site 109-115;	
DEX0443_095.aa.1	Y	0 - o	351-360,1.285; 4-15,1.269; 101-117,1.189; 150-164,1.148; 300-310,1.144; 264-294,1.134; 19-35,1.134; 184-200,1.124; 332-340,1.123; 207-220,1.112; 245-253,1.109; 312-319,1.085; 67-73,1.074; 119-138,1.065; 90-96,1.060; 238-243,1.051; 38-45,1.048; 229-235,1.042; 174-179,1.036	Asp_Protease 98-109; Asn_Glycosylation 95-98; Ck2_Phospho_Site 70-73, 173-176, 180-183, 226-229, 302-305, 331-334, 345-348, 353-356; Myristyl 137-142, 147-152, 151-156, 167-172, 230-235; Pkc_Phospho_Site 36-38, 70-72, 277-279, 353-355, 365-367; Crystallin_Betagamma 238-253; Prokar_Lipoprotein 268-278;	Crystallin; Pepsin (A1) aspartic protease; Eukaryotic and viral aspartic protease active site
DEX0443_097.aa.1	N	0 - o	140-148,1.140; 4-21,1.126; 52-70,1.119; 37-46,1.108; 74-87,1.101; 111-121,1.089; 100-107,1.088; 93-98,1.082; 123-132,1.074	Amidation 140-143; Asn_Glycosylation 34-37, 95-98; Ck2_Phospho_Site 64-67; Glycosaminoglycan 53-56; Myristyl 44-49, 98-103, 137-142; Pkc_Phospho_Site 74-76, 133-135;	
DEX0443_100.aa.1	N	0 - o	51-60,1.178; 62-68,1.130; 30-45,1.109	Asn_Glycosylation 19-22; Ck2_Phospho_Site 60-63, 64-67; Myristyl 17-22, 41-46, 54-59; Pkc_Phospho_Site 47-49;	Lipocalin-related protein and Bos/Can/Equ allergen
DEX0443_102.aa.1	N	1 - o15-37i	163-194,1.164; 148-161,1.149; 97-111,1.142; 69-86,1.136; 129-145,1.136; 34-54,1.104; 13-26,1.100	Ck2_Phospho_Site 87-90, 116-119, 148-151; Myristyl 142-147, 191-196; Pkc_Phospho_Site 45-47;	Binding-protein-dependent transport systems inner membrane component; MAPEG (Membrane-associated proteins in eicosanoid and glutathione metabolism); NULL
DEX0443_102.aa.2	N	0 - i	9-21,1.314; 25-39,1.158	Ck2_Phospho_Site 40-43; Pkc_Phospho_Site 3-5;	
DEX0443_109.aa.1	N	0 - o	15-27,1.138		

Altogether, splice variant sequence analysis, EST support, SAGE tag data, and protein annotation are indicative of SEQ ID NO: 1-248 and encoded protein SEQ ID NO: 249-396 being a diagnostic marker and/or a therapeutic target for cancer.

Example 3b: RT-PCR Analysis

To detect the presence and tissue distribution of a particular splice variant Reverse Transcription-Polymerase Chain Reaction (RT-PCR) is performed using cDNA generated from a panel of tissue RNAs. *See, e.g.*, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press (1989) and; Kawasaki ES *et al.*, *PNAS* 85(15):5698 (1988). Total RNA is extracted from a variety of tissues and first strand cDNA is prepared with reverse transcriptase (RT). Each panel includes 23 cDNAs from five cancer types (lung, ovary, breast, colon, and prostate) and normal samples of testis, placenta and fetal brain. Each cancer set is composed of three cancer cDNAs from different donors and one normal pooled sample. Using a standard enzyme kit from BD Bioscience Clontech (Mountain View, CA), the target transcript is detected with sequence-specific primers designed to only amplify the particular splice variant. The PCR reaction is run on the GeneAmp PCR system 9700 (Applied Biosystem, Foster City, CA) thermocycler under optimal conditions. One of ordinary skill can design appropriate primers and determine optimal conditions. The amplified product is resolved on an agarose gel to detect a band of equivalent size to the predicted RT-PCR product. A band indicated the presence of the splice variant in a sample. The relation of the amplified product to the splice variant was subsequently confirmed by DNA sequencing.

After subcloning, all positively screened clones are sequence verified. The DNA sequence verification results show the splice variant contains the predicted sequence differences in comparison with the reference sequence.

RT-PCR results confirm the presence SEQ ID NO: 1-248 in biologic samples and distinguish between related transcripts.

Example 3c: Secretion Assay

To determine if a protein encoded by a splice variant is secreted from cells a secretion assay is preformed. A pcDNA3.1 clone containing the gene transcript which encodes the variant protein is transfected into 293T cells using the Superfect transfection reagent (Qiagen, Valencia CA). Transfected cells are incubated for 28 hours before the media is collected and immediately spun down to remove any detached cells. The adherent cells are solubilized with lysis buffer (1% NP40, 10mM sodium phosphate pH7.0, and 0.15M NaCl). The lysed cells are collected and spun down and the supernatant extracted as cell lysate. Western immunoblot is carried out in the following

manner: 15µl of the cell lysate and media are run on 4-12% NuPage Bis-Tris gel (Invitrogen, Carlsbad CA), and blotted onto a PVDF membrane (Invitrogen, Carlsbad CA). The blot is incubated with a polyclonal primary antibody which binds to the variant protein (Imgenex, San Diego CA) and polyclonal goat anti-rabbit-peroxidase secondary antibody (Sigma-Aldrich, St. Louis MO). The blot is developed with the ECL Plus chemiluminescent detection reagent (Amersham BioSciences, Piscataway NJ).

Secretion assay results are indicative of SEQ ID NO: 249-396 being a diagnostic marker and/or therapeutic target for cancer.

Example 2: Relative Quantitation of Gene Expression

Real-Time quantitative PCR with fluorescent Taqman® probes is a quantitation detection system utilizing the 5'- 3' nuclease activity of Taq DNA polymerase. The method uses an internal fluorescent oligonucleotide probe (Taqman®) labeled with a 5' reporter dye and a downstream, 3' quencher dye. During PCR, the 5'-3' nuclease activity of Taq DNA polymerase releases the reporter, whose fluorescence can then be detected by the laser detector of the Model 7700 Sequence Detection System (PE Applied Biosystems, Foster City, CA, USA). Amplification of an endogenous control is used to standardize the amount of sample RNA added to the reaction and normalize for Reverse Transcriptase (RT) efficiency. Either cyclophilin, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), ATPase, or 18S ribosomal RNA (rRNA) is used as this endogenous control. To calculate relative quantitation between all the samples studied, the target RNA levels for one sample were used as the basis for comparative results (calibrator). Quantitation relative to the "calibrator" can be obtained using the comparative method (User Bulletin #2: ABI PRISM 7700 Sequence Detection System).

The tissue distribution and the level of the target gene are evaluated for every sample in normal and cancer tissues. Total RNA is extracted from normal tissues, cancer tissues, and from cancers and the corresponding matched adjacent tissues. Subsequently, first strand cDNA is prepared with reverse transcriptase and the polymerase chain reaction is done using primers and Taqman® probes specific to each target gene. The results are analyzed using the ABI PRISM 7700 Sequence Detector. The absolute numbers are relative levels of expression of the target gene in a particular tissue compared to the calibrator tissue.

One of ordinary skill can design appropriate primers. The relative levels of expression of the OSNA versus normal tissues and other cancer tissues can then be determined. All the values are compared to the calibrator. Normal RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

The relative levels of expression of the OSNA in pairs of matched samples may also be determined. A matched pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. All the values are compared to the calibrator.

In the analysis of matching samples, the OSNAs that show a high degree of tissue specificity for the tissue of interest. These results confirm the tissue specificity results obtained with normal pooled samples. Further, the level of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual are compared. This comparison provides an indication of specificity for the cancer state (*e.g.* higher levels of mRNA expression in the cancer sample compared to the normal adjacent).

Altogether, the high level of tissue specificity, plus the mRNA overexpression in matched samples tested are indicative of SEQ ID NO: 1-248 being a diagnostic marker and/or a therapeutic target for cancer.

Example 3: Protein Expression

The OSNA is amplified by polymerase chain reaction (PCR) and the amplified DNA fragment encoding the OSNA is subcloned in pET-21d for expression in E. coli. In addition to the OSNA coding sequence, codons for two amino acids, Met-Ala, flanking the NH_2-terminus of the coding sequence of OSNA, and six histidines, flanking the COOH-terminus of the coding sequence of OSNA, are incorporated to serve as initiating Met/restriction site and purification tag, respectively.

An over-expressed protein band of the appropriate molecular weight may be observed on a Coomassie blue stained polyacrylamide gel. This protein band is confirmed by Western blot analysis using monoclonal antibody against 6X Histidine tag.

Large-scale purification of OSP is achieved using cell paste generated from 6-liter bacterial cultures, and purified using immobilized metal affinity chromatography (IMAC). Soluble fractions that are separated from total cell lysate were incubated with a nickel

chelating resin. The column is packed and washed with five column volumes of wash buffer. OSP is eluted stepwise with various concentration imidazole buffers.

Example 4: Fusion Proteins

The human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5'and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector. For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 2, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced. If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. *See, e.g.*, WO 96/34891.

Example 5: Production of an Antibody from a Polypeptide

In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100, µg/ml of streptomycin. The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP20), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands *et al.*, *Gastroenterology* 80: 225-232 (1981).

The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide. Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step

procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

Example 6: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA is isolated from individual patients or from a family of individuals that have a phenotype of interest. cDNA is then generated from these RNA samples using protocols known in the art. *See*, Sambrook (2001), *supra*. The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO: 1-248. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky *et al.*, *Science* 252(5006): 706-9 (1991). *See also* Sidransky *et al.*, *Science* 278(5340): 1054-9 (1997).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons are also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing. PCR products is cloned into T-tailed vectors as described in Holton *et al.*, *Nucleic Acids Res.*, 19: 1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements may also be determined. Genomic clones are nick-translated with digoxigenin deoxyuridine 5' triphosphate (Boehringer Manheim), and FISH is performed as described in Johnson *et al.*, *Methods Cell Biol.* 35: 73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C-and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. Johnson (1991). Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 7: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

Antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described above. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced. The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide. Next, 50 µl of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate. 75 µl of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution are added to each well and incubated 1 hour at room temperature.

The reaction is measured by a microtiter plate reader. A standard curve is prepared, using serial dilutions of a control sample, and polypeptide concentrations are plotted on the X-axis (log scale) and fluorescence or absorbance on the Y-axis (linear scale). The concentration of the polypeptide in the sample is calculated using the standard curve.

Example 8: Formulating a Polypeptide

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the

individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1, μg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 μg/kg/hour to about 50 mg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U. S. Pat. No.3,773,919, EP 58,481, the contents of which are hereby incorporated by reference herein in their entirety), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22: 547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15: 167-277 (1981), and R. Langer, Chem. Tech. 12: 98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the

secreted polypeptide are prepared by methods known per se: DE Epstein et al., Proc. Natl. Acad. Sci. USA 82: 3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324, the contents of which are hereby incorporated by reference herein in their entirety. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation.

For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides. Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably, the carrier is a parenteral carrier, more preferably, a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e. g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1 % (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container (s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

Example 9: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is

in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided above.

Example 10: Method of Treating Increased Levels of the Polypeptide

Antisense or RNAi technology are used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided above.

Example 11: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e. g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks. pMV-7 (Kirschmeier, P. T. et al., DNA, 7: 219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5'and 3'end sequences respectively as set forth in Example 3. Preferably, the 5'primer contains an EcoRI site and the 3'primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and

the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB 101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+aml2 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media.

If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 12: Method of Treatment Using Gene Therapy-In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide.

The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, Tabata H. *et al. Cardiovasc. Res.* 35 (3): 470-479 (1997); Chao J

et al. Pharmacol. Res. 35 (6): 517-522 (1997); Wolff J. A. *Neuromuscul. Disord.* 7 (5): 314-318 (1997), Schwartz B. *et al. Gene Ther.* 3 (5): 405-411 (1996); and Tsurumi Y. *et al. Circulation* 94 (12): 3281-3290 (1996); WO 90/11092, WO 98/11779; U. S. Patent No. 5,693,622; 5,705,151; 5,580,859, the contents of which are hereby incorporated by reference herein in their entirety.

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, ovarian, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P. L. *et al. Ann. NY Acad. Sci.* 772: 126-139 (1995) and Abdallah B. *et al. Biol. Cell* 85 (1): 1-7 (1995)) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, ovarian, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to

the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 μg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to ovarians or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle in vivo is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice.

The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 13: Transgenic Animals

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e. g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (I. e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., *Appl. Microbiol. Biotechnol.* 40: 691-698 (1994); Carver et al., *Biotechnology* 11: 1263-1270 (1993); Wright et al., *Biotechnology* 9: 830-834 (1991); and U. S. Pat. No. 4,873,191, the contents of which is hereby incorporated by reference herein in its entirety); retrovirus mediated gene transfer into germ lines (Van der Putten et al., *Proc. Natl. Acad. Sci., USA* 82: 6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., *Cell* 56: 313-321 (1989)); electroporation of cells or embryos (Lo, 1983, *Mol Cell. Biol.* 3: 1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e. g., Ulmer et al., *Science* 259: 1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm mediated gene transfer (Lavitrano et al., *Cell* 57: 717-723 (1989). For a review of such techniques, see Gordon, "Transgenic Animals," *Intl. Rev. Cytol.* 115: 171-229 (1989).

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell *et al., Nature* 380: 64-66 (1996); Wilmut *et al., Nature* 385: 810813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, I. e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e.g., head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., *Proc. Natl. Acad. Sci. USA* 89: 6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., *Science* 265: 103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 14: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (E. g., see Smithies et al., Nature 317: 230-234 (1985); Thomas & Capecchi, Cell 51: 503512 (1987); Thompson et al., Cell 5: 313-321 (1989)) Alternatively, RNAi technology may be used. For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention in vivo. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e. g., see Thomas & Capecchi 1987 and Thompson 1989, supra). However, this approach can be routinely adapted for

use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site in vivo using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e. g., knockouts) are administered to a patient in vivo. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e. g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered in vitro using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e. g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e. g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U. S. Patent No. 5,399,349; and Mulligan & Wilson, U. S. Patent No. 5,460,959, the contents of which are hereby incorporated by reference herein in their entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

While preferred illustrative embodiments of the present invention are described, one skilled in the art will appreciate that the present invention can be practiced by other than the described embodiments, which are presented for purposes of illustration only and not by way of limitation. The present invention is limited only by the claims that follow.

We claim:

1. An isolated nucleic acid molecule comprising:

(a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 249-396;

(b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248;

(c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or

(d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b).

2. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a cDNA.

3. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is genomic DNA.

4. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is an RNA.

5. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a mammalian nucleic acid molecule.

6. The nucleic acid molecule according to claim 5, wherein the nucleic acid molecule is a human nucleic acid molecule.

7. A method for determining the presence of a ovarian specific nucleic acid (OSNA) in a sample, comprising the steps of:

(a) contacting the sample with the nucleic acid molecule of SEQ ID NO: 1-248 under conditions in which the nucleic acid molecule will selectively hybridize to a ovarian specific nucleic acid; and

(b) detecting hybridization of the nucleic acid molecule to a OSNA in the sample, wherein the detection of the hybridization indicates the presence of a OSNA in the sample.

8. A vector comprising the nucleic acid molecule of claim 1.

9. A host cell comprising the vector according to claim 8.

10. A method for producing a polypeptide encoded by the nucleic acid molecule according to claim 1, comprising the steps of:

(a) providing a host cell comprising the nucleic acid molecule operably linked to one or more expression control sequences, and

(b) incubating the host cell under conditions in which the polypeptide is produced.

11. A polypeptide encoded by the nucleic acid molecule according to claim 1.

12. An isolated polypeptide selected from the group consisting of:

(a) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 249-396 ; or

(b) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248.

13. An antibody or fragment thereof that specifically binds to:

(a) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 249-396 ; or

(b) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248.

14. A method for determining the presence of a ovarian specific protein in a sample, comprising the steps of:

(a) contacting the sample with a suitable reagent under conditions in which the reagent will selectively interact with the ovarian specific protein comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 249-396; and

(b) detecting the interaction of the reagent with a ovarian specific protein in the sample, wherein the detection of binding indicates the presence of a ovarian specific protein in the sample.

15. A method for diagnosing or monitoring the presence and metastases of ovarian cancer in a patient, comprising the steps of:

(a) determining an amount of:

(i) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 249-396;

(ii) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248;

(iii) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (i) or (ii);

(iv) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (i) or (ii);

(v) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 249-396 ; or

(vi) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248 and;

(b) comparing the amount of the determined nucleic acid molecule or the polypeptide in the sample of the patient to the amount of the ovarian specific marker in a normal control; wherein a difference in the amount of the nucleic acid molecule or the polypeptide in the sample compared to the amount of the nucleic acid molecule or the polypeptide in the normal control is associated with the presence of ovarian cancer.

16. A kit for detecting a risk of cancer or presence of cancer in a patient, said kit comprising a means for determining the presence of:

(a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 249-396;

(b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248;

(c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or

(d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b); or

(e) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 249-396 ; or

(f) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248.

17. A method of treating a patient with ovarian cancer, comprising the step of administering a composition consisting of:

(a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 249-396;

(b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248;

(c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b);

(d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b);

(e) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 249-396 ; or

(f) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-248;

to a patient in need thereof, wherein said administration induces an immune response against the ovarian cancer cell expressing the nucleic acid molecule or polypeptide.

18. A vaccine comprising the polypeptide or the nucleic acid encoding the polypeptide of claim 12.

5

SEQUENCE LISTING

<110> diaDexus, Inc.
Macina, Roberto
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Liu, Chenghua
Sun, Yongming
Turner, Leah

<120> Compositions and Methods Relating to Ovarian Specific Genes and Proteins

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<223> n=a, c, g or t

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<213> Homo sapien

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<400> 131
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<213> Homo sapien

<400> 133
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<400> 134
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agagaccacc aaggtggaaa tgctgagact ttctctggca cgaaatcttg ctcgggcaat 2160

tataagagaa ggctcactgg aaggttcctg agaactgctt caatgtggta tctttgtatg 2220

gcaatgtata tagatttttt aaaagaataa atgttgtttt gcaaatg 2267

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<211> 548
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<213> Homo sapien

<400> 187
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atgatcataa tagatgttaa attttttttt tctgtttggt ttcagaaaaa tcagagatgg 180

tgccaagttg ccccttttatc tatatcatcc gtaaggatgt agatgtttac tctcaaatct 240

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tcatcagagc atgtatggag gaaatgcacc aggttgcaat tgctgctaaa gatccagcca 420

atggccgcca gttcagcagc caggtctcca ttttgtcagc aatggagctc atctggaacc 480

tgtgtgagat tctttttatt gaagtggccc caggtaggca tggaatatct caccataatc 540

tcataggt 548

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<211> 1359
<212> DNA
<213> Homo sapien

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tgagggtttg ggcttgcagg cgctgcagga gacgcccagg cggagtcttg tctcgcagcc 180

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tgcctgtgtg gcctaaggtt tattcaacgt attatctcag gagactattc ctgttttatc 720

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<213> Homo sapien

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<223> n=a, c, g or t

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ttttactttg ggacagaatt tttatttgta tagagtgctt actaattgtt aaatagttca 180

gagtatataa ctatttactt taaggactca tggtaggttt aagggtggaa atgagttggt 240

gtcatttcaa ttacaaagat aaaagtttgc catatannnn nnnnnnnnnn nnnnnnnnnn 300

tggtagtgta catagtagtc atcaagtctt ttgacagaag tatattttta aagaattcat 360

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<212> DNA

<213> Homo sapien

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cttagggcct ggtcgggggа ggaaaagttg taaacaaatt gccaccttaa attcgcggtg 180

cgagtctgcg gagctgccgg gttcattgtg tttacgaggc tcgctgaaat gtgtggaatc 240

cagggaaggc gagcacccag acgggggccc gccggggccg cggccagcgc cggggaaatg 300

ccgcgccggg gagcagcctg cgccggcctg agcccttccc tttgcactcg gctgtttttt 360

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cacaaatatt gtcgtaagtt gcagctggct gccccacttc ctaattcagc tcacacagcc 480

tctccccacg ctatggaaat gcgtcgggag tgaactccgg cggccgcgct caccacgtgg 540

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ctggggtgaa tattgtctgt gtcgagtggt ttctctcctc tctacctcgg cttcctcttc 780

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tcagatccgc cggggctgca gtctcgaggg cgagtccgtg tgccgcggcc acccgcgccc 960

ccacggctgt tgggggctca ccgggcgggt gcgcgcaagc gggcgtgggc gcgcgggccg 1020

cgactccccg gcgctcactc ctc 1043

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<211> 955
<212> DNA
<213> Homo sapien

<220>
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<222> (564)..(588)
<223> n=a, c, g or t

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<213> Homo sapien

<400> 192
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gaaaagtgag aggtcagact cctaaggtgg ccaaacagga gaagaagaag aagaagacag 120

gtcgggctaa gcggcggatg cagtacaacc ggcgctttgt caacgttgtg cccacctttg 180

gcaagaagaa gggccccaat gccaactctt aagtcttttg taattctggc tttctctaat 240

aaaaaagcca cttagttcag 260

<210> 193
<211> 187
<212> DNA
<213> Homo sapien

<400> 193
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aactcatgca gatgcagcat tcctgcgtct gtggggaccc tctggccgga gggctccctg 120

gtgtgcttcc tgcacaccgt ggacaggtga ctgtatggta tgagactgtg atcggtggga 180

acttttg 187

<210> 194
<211> 2206
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<213> Homo sapien

<220>
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<222> (1423)..(1725)
<223> n=a, c, g or t

<400> 194
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aacatttgag agctaactat atttttataa gactactata caaactacag agtttatgat 2040

ttaaggtact taaagcttct atggttgaca ttgtatatat aatttttaa aaaggttttc 2100

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<211> 600
<212> DNA
<213> Homo sapien

<400> 195
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acgagcagag aactcacagc tcaccaccaa acgagacgcg cacaacatcc cgcgccaact 180

cccacacagc aaatacaagg gcgactaaac aggacaagcg agaacagaca ccactgcttg 240

aagccaaaca aaggggacaa caagagcaaa gaacacacgc gaaaccacgc aaccatagag 300

cccgcagctc tgcagggcag ttagaaacac caaaaagggc atacagcacc cccacaggac 360

agcaaagaca atcaacagac acaaccagaa cgcagacaca agaaaagaaa gatagggaga 420

aacacccgcg aaccaggaca aaaacaacaa caacacagga cggaacaccc cacaggacaa 480

caactaccac agctagcgca agacaactgg acacaaaccc agagacaggc tccgccgcga 540

cacgccgcca agcaaaaacc acatacagag aagcaagaga gcacaacaca agacacacaa 600

<210> 196
<211> 4213
<212> DNA
<213> Homo sapien

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<223> n=a, c, g or t

<220>
<221> misc_feature

<222> (1253)..(1253)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (1259)..(1259)
<223> n=a, c, g or t

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<210> 197
<211> 6537
<212> DNA
<213> Homo sapien

<220>
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<222> (3557)..(3557)
<223> n=a, c, g or t

<220>
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<222> (3571)..(3571)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (3577)..(3577)
<223> n=a, c, g or t

<400> 197
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acctctaaac ataatgattt ttttcatcta caaaaatttc tgttatacta gaaaatttgc 180

agaagacatt tttttcttgt gacattaaat gtacattatt tacagttgaa aagtaatcta 240

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<213> Homo sapien

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ccagcctgct ccacccagag aagcatattt tgtgagaacc agtgggaagg agcctgagct 540

gctggaacct attccctatg aattcatggc ataataggtg ttaaaaaaat aaaagacttc 600

tggactgtta aaaaaaaaaa aaaggttaaa taattttccc aaggtcacaa agctgttggg 660

taaaacagcg tattgtgttt tcccaagcct tgccttgttt cttcattcat ttttatttaa 720

caataatttc ttgagttatc taccacagac taagtgttat tctaaggcac ataagatttg 780

tccatgaaga aaacagaaaa aaacacattg tggcttcatg gagtttattt tcccacagac 840

aataagcaac aatttttata acagaaggaa gtga 874

<210> 208
<211> 2244
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (962)..(962)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (980)..(980)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (984)..(984)
<223> n=a, c, g or t

<400> 208
gctctgtgaa ggcacggtat gaggctagag gagccctggg tctgccttta cttacccggg 60

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gcttttgggt ggggtttccc acccaagttc aagaggagga gcagacatct gtctctgccc 180

ccttcctttg gtcttcttcc tccaggatct gtgtctcagc tcctgcctct cactccctct 240

ctatctgcct tctgtttctc tttgggtctc tcctgctctc ctctttctgg cctgcctcct 300

ctctctaatc ctgcctctct tcctctcccc cccttgcctt gccccctctc actctaggcc 360

ctcagctcca gcctctggcc ctgacctcga gctgtgtcct gattctgtct ctgccccagg 420

actgcagggc tccaggaggt ctgggctgcc tccagcttcc cactcccagg ttgcggctgg 480

actgggactg gttcctttcc agttgaatct ggcagccaaa cctctcctcc ccctcacctg 540

acaggtgcag cggcctggct ggggagcccg cccgccggcc ggccagggat ggaagcgaca 600

ggaatctcat tagcatctca attaaaggtg cctccatatg cgtcggagaa ccagacctgc 660

agggaccagg aaaaggaata ctatgagccc cagcaccgca tctgctgctc ccgctgcccg 720

ccaggcacct atgtctcagc taaatgtagc cgcatccggg acacagtttg tgccacatgt 780

gccgagaatt cctacaacga gcactggaac tacctgacca tctgccagct gtgccgcccc 840

tgtgacccag tgatgggcct cgaggagatt gcccccctgca caagcaaacg gaagacccag 900

tgccgctgcc agccgggaat gttctgtgct gcctgggccc tcgagtgtac acactgcgag 960

cnactttctg actgcccgcn tggnactgaa gccgagctca aagatgaagt tgggaagggt 1020

aacaaccact gcgtcccctg caaggcaggg cacttccaga atacctcctc ccccagcgcc 1080

ctgctgccag ccccacacca ggtgtgagaa ccaaggtctg gtggaggcag ctccaggcac 1140

tgcccagtcc gacacaacct gcaaaaatcc attagagcca ctgcccccag agatgtcagg 1200

atcgctgctc aagaggcgtc cgcagggaga gggacccaat cctgtagctg gaagctggga 1260

gcctccgaag gcccatccat acttccctga cttggtacag ccactgctac ccatttctgg 1320

agatgtttcc ccagtatcca ctgggctccc cgcagcccca gttttggagg caggggtgcc 1380

gcaacagcag agtcctctgg acctgaccag ggagccgcag ttggaacccg gggagcagag 1440

ccaggtggcc cacggtacca atggcattca tgtcaccggc gggtctatga ctatcactgg 1500

caacatctac atctacaatg gaccagtact ggggggacca ccgggtcctg gagacctccc 1560

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tgccacaccc tctaacaggg gcccaaggaa ccaatttatc acccatgact gactgagtct 1740

gagaaaaggc agaagaaggg gggcacaagg gcaccttctc ccttgaggct gccctgccca 1800

cgtgggattc acaggggcct gagtagggcc cggggaagca gagccctaag ggattaaggc 1860

tcagacacct ctgagagcag gtgggcactg gctgggtacg gtgccctcca caggactctc 1920

cctactgcct gagcaaacct gaggccacac ggtcacctgc aaggacgtca cgggcccctc 1980

taaaggattc gtggtgctca tccccaagct tcagagaccc tttggggttc cacacttcac 2040

gtggactgag gtagaccctg catgaagatg aaattatagg gaggacgctc cttccctccc 2100

ctcctagagg agaggaaagg gagtcattaa caactagggg gttgggtagg attcctaggt 2160

atggggaaga gttttggaag gggaggaaaa tggcaagtgt atttatattg taaccacatg 2220

caaataaaaa gaatgggacc taga 2244

<210> 209
<211> 299
<212> DNA
<213> Homo sapien

<400> 209
ggacccatcc aacgatacca ggagagtcat ccaacctgtg acacaaccaa tccgatacta 60

caatcctcca ttaactgaac ccactcgtcg cttacaacag tgactaacca tagacaacga 120

catcacgcaa acacatacaa gaggatcact cactagctag ccataactcg acatatgccc 180

actgccatca gacaacacta actcatccta caatatcccg aaatataaag caaaacgcat 240

acagcactcc acgaacactg accatcaaaa tacaaccgac aacactcccc agaacaaca 299

<210> 210
<211> 491
<212> DNA
<213> Homo sapien

<400> 210
agtggttcca agaatgtacg aggaagcgag agaaggtata aagtatggag agggtcagtg 60

aaaggtatca tggctggggg atatgtagaa tatgtggagt agaatgggag tctgttaaac 120

aatatagtga gtaagcgatt aaatttatta tcatgcgagg tattttacca gatgatgtgt 180

cctagttcag cagtattgtc aacgtatgca aagataaggc ttactgttga ttatctaatg 240

agtcagtcaa tgaaagtgat gtaaggaggg cctgagagaa ttgtgtgcca tttctgcagt 300

tgcggatagt gaactgacct ggcaaaaggt ttacataaat accgtactca actgtgggga 360

gtttaaatgt ctggtggctg ccgtgctgag ttgtcaagaa attaaagctg caagaggact 420

ccaaggaggc aaaagaaaaa acaatataga ggggtggagg ttgttaagaa atttcaattc 480

aaaaatgcca a 491

<210> 211
<211> 375
<212> DNA
<213> Homo sapien

<400> 211
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ccacagccga cacacagacc gcaggagccg cacgccagac acagccgccc cgccaccgca 120

cccgcccaca caggcccgaa cgaggcagcg aacgcagcgc agggaagacg caggcaaccg 180

aagcgacacg acacccagac caaccaacga acccacacaa cgagagacaa ccgaacaaca 240

accaggccag agacgacacc aagacacagc ccggacaggc aacgaagacg ccgcaaagaa 300

cgccgccccg aacaaagcag acgcaaaagg aggcagagcc accgcggcga gcgcagaaac 360

agaggcaagc gagag 375

<210> 212
<211> 1052
<212> DNA
<213> Homo sapien

<400> 212
tttactgctg tattccaagc agaaaggttg gcatacagga gacctcaaaa atacgctact 60

ttgatcttga ggagagtgaa aaatcttact cattttatgt acaaagcaca gatgtgcata 120

cattatataa aaagaaatag tttacgtatg gcattaagat ttcatgaaga ttagaaaaac 180

aatgtttaca aaaggtcctt acaaaggtag taattcaaga aaagatcaat aaacgatgtg 240

ttaaagtaag atttttggaa gctcaaattc aggcaataca aaagccagca atatatcttg 300

ctactcgaat gcctctattt cacctcaaac tcacagataa aactgaaccc aatatgtcct 360

tgtccattaa aaagcaaatc accaagaaag ctaacaaaag attcccttca atgtctcttt 420

tattgacagt ggtcccaaaa ctcctggtca atgaattcaa aacccaaatc ttgcaggtag 480

gacttaacct catctgctgc caaatagctg gctatgtgac cttgggcaga gccacagcct 540

cccgcgcctc gctcagctcc aacatggcaa aaatctccag ccctacagag actgagcggt 600

gcatcgagtc cctgattgct gtcttccaga agtatgctgg aaaggatggt tataactaca 660

ctctctccaa gacagagttc ctaagcttca tgaatacaga actagctgcc ttcacaaaga 720

accagaagga ccctggtgtc cttgaccgca tgatgaagaa actggacacc aacagtgatg 780

gtcagctaga tttctcagaa tttcttaatc tgattggtgg cctagctatg gcttgccatg 840

actccttcct caaggctgtc ccttcccaga agcggacctg aggacccctt ggccctggcc 900

ttcaaaccca ccccctttcc ttccagcctt tctgtcatca tctccacagc ccacccatcc 960

cctgagcaca ctaaccacct catgcaggcc ccacctgcca atagtaataa agcaatgtca 1020

ctttttttaaa acatgaaaaa aaacaaaaaa gg 1052

<210> 213
<211> 199
<212> DNA
<213> Homo sapien

<400> 213
ggccactcca gaacagtacc agatcctgaa gaaggaggct gagaaagtgg cccgggtgaa 60

ggcgctatat gaggagctgg atctgccagc agtgttcttg caatatgagg aagacagtta 120

cagccacatt atggctctca ttgaacagta cgcagcaccc ctgcccccag ccgtctttct 180

ggggcttgcg cgcaaaatc 199

<210> 214
<211> 289
<212> DNA
<213> Homo sapien

<400> 214
aaacccgaca ggacatactc aacgataccg aagcagtatc acccactgga aacatccctc 60

agttgcagcc tcatcctgct ccagaccctg cacgctctac cgggatacgc tgatccggcc 120

ctcaaactcc acctatcacg gaacagcgag agcgccgaac cctacaataa gcacccagcc 180

atgtcaaggt aatcatcgag catagcgtgt agcgtccgtc cgagaccaag cctgcgctcg 240

atgagcctga aacacacacg tccacgacca aaccgcccgg ccgaacacg 289

<210> 215
<211> 415
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (277)..(300)
<223> n=a, c, g or t

<400> 215
ctttgctgat atttataatt tggtatcata agaatgtttt cctctacagt atttgtcatg 60

ccagtttata acaaaaaaaa atgcagggat tttatttcta tgggaaactt tacagctatg 120

ttttactttg ggacagaatt tttatttgta tagagtgctt actaattgtt aaatagttca 180

gagtatataa ctatttactt taaggactca tggtaggttt aagggtggaa atgagttggt 240

gtcatttcaa ttacaaagat aaaagtttgc catatannnn nnnnnnnnnn nnnnnnnnnn 300

tggtagtgta catagtagtc atcaagtctt ttgacagaag tatattttta aagaattcat 360

ctgtgatgaa tccataatgt ctggaacttt gctgagactt gagtgggccc agttt 415

<210> 216
<211> 610
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (459)..(459)
<223> n=a, c, g or t

<400> 216
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gcgaactggg cctttagatg catgctccga gcggccgcag tgtgatggat gagcggccgc 120

ccgggcaggg ttgcacgctg cctgcatgtg tcttgaacat ttcctgtgtg cctttctcaa 180

gcgagaggat gtagcccagc gaactgtgtc cccgactcat gtctttgagc gagcccactt 240

ctcgctggat tgtgtcctac tgcgcctcat gaggcgtccg tggagccatc catcgcttgt 300

cttaatccgt cctgctgctg ctgccgcttc cggcgctcag cgtcgccaca ccgtttggac 360

cctgaggctc gctcagattg atgagctcct ctctggctca gacactcgct ggaggaatga 420

atagccaggc tctgacctca agcaaggcat gaactcagnc tttattaaga aaattcacat 480

tttccagggg cagcagaccg ggatcgatgc gtggcgcttg tctcctgttg cccacaccgt 540

cttcgaaatc tctgttactg ctcccagatg cccttctagt attcactgct ctctctcgat 600

tcttgatttt 610

<210> 217
<211> 1435
<212> DNA
<213> Homo sapien

<400> 217
gctttttttt ttttttttt ttttttttaa ataagaaaaa cccggtaatg attttcgggg 60

ttgtagagga aataggagag aaaatggggg gaaataggtg tattaaacta taagggtttt 120

tccctcggtg taaatagagg gtttaatgtt gtaaatggtg gtgtggggtg aaggtgtgcc 180

ccattgtggt ggtgggtggt taaatactgt taaagggtac tactagggct ggtaactagc 240

tagtggtgga gttccgtgtt aagataggag ggctgatatg tgtgactcag ggaaaacggt 300

ggttcactac ccacagaaga gtttcttccc agtatagggt taactagcgg gcggggctta 360

cagcgcgacg cagttcaacg cgaagcctct gtgcctaaca aagcttcctc cacaaacgtc 420

tctatcacag cgcgggacgc tcacagtttg tgaaaagtcc ctctgaacaa aaaggctatc 480

acctgacatg ccccacctgg gtcacgtgcc cgtccgatac ttttctgaac atatgtgccc 540

aagcgcccaa caatccttca cttcccggca tgtgtaaacg caccagtggg gcgcgcaagt 600

acactcgaca aaacatgacg tgagcccccg gacaaaaccg tggggcggtc aacccacact 660

gggcccaaca agcgtggtat ccctggtggt gcgaccattg cggtcactcc cggcgtccca 720

caactgtccc accacaacac caaccgtcaa gccacaccac accacaccaa ccacaaacac 780

acaccccaca tcaccaccac ccacacccca ccaccaacac aacacttaac acaacgatac 840

cctaacccac cctcactcaa cactacacaa ctacaacaac cccctaccta caacaccgaa 900

ctctaatctt caacctacac tcacacatca caataacata aatatatacc ctcttctcca 960

cacaccctac cctccactac tctcacttcc acatctccaa tcacaactac ctctcaactc 1020

cctcctacta tacacatcac acacatatta acataccccc catccccacc ccccactact 1080

catcactaca caccctaacc accctaccaa acaactccac caataaccca aaccgataat 1140

cccactaaca ccatccactc agtagacact accaatccca atctacaaca tccacattcc 1200

cacacactcc actcccccac tactaacttt acaacacacc accacccata cacatcttct 1260

acaccaccct catacccaca tacaacaaca taaaaactca accacaccac aataacccaa 1320

cacaaaaacc accccaccct acaccactaa caccacatca cacacccccc acactcaaca 1380

cacaaacaca accacacaac aaaacacgac ctcccccacc acccctcaca caccc 1435

<210> 218
<211> 534
<212> DNA
<213> Homo sapien

<400> 218
ataaatttga tcctggctgt ggtggacatg gtctacgagg aacagaatca ggccaccttg 60

gaagaagcag aacagaaaga ggccgaattt cagcagatga ttgaacagct taaaaagcaa 120

caggaggcag ctcaggcagc aacggcaact gcctcagaac attccagaga gcccagtgca 180

gcaggcaggc tctcagacag ctcatctgaa gcctctaagt tgagttccaa gagtgctaag 240

gaaggaagaa atcggaggaa gaaaagaaaa cagaaagagc agtctggtgg ggaagagaaa 300

gatgaggatg aattccaaaa atctgaagct ggggacccac acggcagagc catggtactg 360

gaggagccat taacaaagct ttcaataaac ctctctttct tgaagttacc tgagaatgga 420

tccattccct gcaactgaag attctaagga actgggtttc tcagtataca atgggaatgg 480

ttgggaggag gtaaagagta gaagacagta tcaagaatcc agagcccagc acct 534

<210> 219
<211> 173
<212> DNA
<213> Homo sapien

<400> 219
catcagcagg cgcgggcgcc accgcgggcc cacgcggcac ccgtgggcga cacggtaccc 60

cggtcacact ccacaaattg ccgcacaacc ggcgaccaga gaagaagccg ccagcaagcg 120

ccagaccgcc agcacgacgt aaccaacgac ctaccacaca cagacgcaac cag 173

<210> 220
<211> 515
<212> DNA
<213> Homo sapien

<400> 220
tgcgtatgct cggcgttatt tccactagag actactacag cgcaatactg acgcatacaa 60

aacactctta gagcataaca acagacacac gtagactaca caacccagaa aaagaacaat 120

aataaaaaga ataaacacta catagtaaac acccacatag agaaagcaca accaacacag 180

aacacgcaac atcccacacg aaaaccagac aacaccacga accacagaca cacagcgcca 240

cacacagaag accgcagacc gaacacaaca cgacccatac aagaacaaag aaccacgcga 300

caggcaccaa acaaacgaca tcacaccagc caagacacca gaaacaaagc acataaacaa 360

cggaaacgaa agatcacgca cacgacaacc accacacacc acaccacgac agcacagcaa 420

acgagacacc ccacccacac aaacgcgaca acacgaccca aaacgcacaa ccacaaacca 480

accacacaga acaacaacac aaccaaaaca acaca 515

<210> 221
<211> 261
<212> DNA

<213> Homo sapien

<400> 221
aaaaagaatg gaacaacttc agtaagaaga acatttttca ttttagattt ctatgcctta 60

ttttactagt tgattccagg cgtgaattcc aagaagaacc aaatgtattt tgactggggt 120

ccaggggaga tgctggtatg tgaaacctcc ttcaacaaaa aaggtagggt ttttttttctt 180

ccaaattatc catcttggca catttggttg tttttctgtt tattacctca gattttacta 240

gttgtggact gaaacagttg a 261

<210> 222
<211> 284
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (162)..(162)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (172)..(172)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (230)..(230)
<223> n=a, c, g or t

<400> 222
cttttgtctt tccgtggagc tgtcgccatg aaggtcgagc tgtgcagttt tagcgggtac 60

aagatctacc ccggacacgg gaggcgctac gccagggacc gacgggaagg ttttcccagt 120

ttcttaatgc gaaatgcgga gttcggcttt tccttttcca angagggaat tncctcggca 180

agattaaact tgggacttgt ccctcttacc aggaagggaa ggcaccaaan aaaggggacc 240

agttcgggaa aggaaaattt tcaaaaaagg aaaaaaggaa cccc 284

<210> 223
<211> 424
<212> DNA
<213> Homo sapien

<400> 223
gaggtctgtg aggaccaatt tgtgggtagt tcatcttccc tcgattggtt aactccttag 60

tttcagacca cagactcaag attggctctt cccagagggc agcagacagt caccccaagg 120

caggtgtagg gagcccaggg aggccaatca gccccctgaa gactctggtc ccagtcagcc 180

tgtggcttgt ggcctgtgac ctgtgacctt ctgccagaat tgtcatgcct ctgaggcccc 240

ctcttaccac actttaccag ttaaccactg aagcccccaa ttcccacagc ttttccatta 300

aaatgcaaat ggtggtggtt caatctaatc tgatattgac atattagaag gcaattaggg 360

tgtttcctta agcaactaca caccaacctg ctggctttag aataaaagcc ccaactgaac 420

tgag 424

<210> 224
<211> 314
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (307)..(307)
<223> n=a, c, g or t

<400> 224
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gtggaacagc acaatgttgg aaagatccaa ataatgactt cagaaaaaac ttgaaagtaa 120

cagcagtgcc tacactactt aagtatggaa cacctcaaaa actggtagaa tctgagtgtc 180

ttcaggccaa cctggtggaa atgttgttct ctgaagatta agattttagg atggcaatca 240

tgtcttgatg tcctgatttg ttctagtatc aataaactgt atacttgctt tgaattcatg 300

ttagcantaa atga 314

<210> 225
<211> 2528
<212> DNA
<213> Homo sapien

<400> 225
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ccctacattt ctttttttaa taatgataaa catgcaactt ttttgtagct ttacaacaaa 120

tacccagatg ctgtggccac atggctaaac cctgacccat ctcagaagca gaatctccta 180

gccccacagg tatttttaaa cttctcataa ttaaactaca gtgatgaaag atagccacac 240

tcaggccatt tgggctgctc agatgaatcc tgcctgcctg ctggcaaaca tgtgcttagg 300

acattgactg atctgccatg ttggcttctc tctgtgttaa gccatccaca gatgaggctg 360

aaaaataaaa actgctttgg attaaaaagg ttaacttttg aataaaaaag ctaggcatgt 420

gtgatgcgca ctaacacgtg ccattccttc ttcagaatgc tgtgtcctct gaagaaacca 480

atgactttaa acaagaggta agttctcatt ttcaatcaga ggcccatcat gccttgaaga 540

gatgaaagaa ggcattgcct ggattctctt ctgatgaaat ttcattagca agttttccag 600

ctaattggca gtctaaaact tgctcataaa taaaacatgt atttactaaa tatcagaaat 660

actaggtttc ctcggataag tttagcatta cagaagatgt ttattaatgc ctgttatttg 720

aaacattaat ctgcttgcaa tttatttaag gtattttgta gatatctaat atctaataag 780

catctaatta atgcgtatca aagctaagat tttgccttta ggaaagtttt ctttcctaat 840

aaaatagttt atttgacaac tattcttttt attaggatca ttcatatatt tgctaagcaa 900

agagtaaatt tattttcctt aagattcaat ttgaatatac taagaatatt aaagcaagtt 960

agataaatta cccaatatat ttgtcaattt gaaatttgat agacattagt tgtttaattc 1020

aatgggcagt tttgagctgc agtttataca cacatgcata acagagtcac ctttcaatta 1080

tccatgttaa taggaaagtg gttatagatt ttagtacaca cattaaaata tggatactct 1140

tctcttttga taaatctcat ttcaaataaa aaaaccagtc tcataattat gtatctgtat 1200

ctattacatc attgaattta gtaaataatg tttaatatgt ataaggaaaa acaatgttat 1260

tgacatgaag attatactca catatttggc ttgaaaatat ctataaaaat aatttctgtt 1320

gcaaagtaag aaatgttctt cagaatgtta ttaatccctg tgttaaaaga gaaattggaa 1380

gatgctcact ttagctccta aaagccatgg tatgtactgt gaatgcaaag attctgaaac 1440

taaataaaaa gaaagatagt aaaagactaa tgtgctataa aggctaaggg aaaataaaaa 1500

cccatatatt aattttcccg gccatcttaa ttttcagacc cttccaagta agtccaacga 1560

aagccatgac cacatggatg atatggatga tgaagatgat gatgaccatg tggacagcca 1620

ggactccatt gactcgaacg actctgatga tgtagatgac actgatgatt ctcaccagtc 1680

tgatgagtct caccattctg atgaatctga tgaactggtc actgattttc ccacggacct 1740

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tgatagtgtg gtttatggac tgaggtcaaa atctaagaag tttcgcagac ctgacatcca 1860

gtaccctgat gctacagacg aggacatcac ctcacacatg gaaagcgagg agttgaatgg 1920

tgcatacaag gccatccccg ttgcccagga cctgaacgcg ccttctgatt gggacagccg 1980

tgggaaggac agttatgaaa cgagtcagct ggatgaccag agtgctgaaa cccacagcca 2040

caggcagtcc agattatata agcggaaagc caatgatgag agcaatgagc attccgatgt 2100

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tcgtatttct catgaattag atagtgcatc ttctgaggtc aattaaaagg agaaaaaata 2280

caatttctca ctttgcattt agtcaaaaga aaaaatgctt tatagcaaaa tgaaagagaa 2340

catgaaatgc ttctttctca gtttattggt tgaatgtgta tctatttgag tctggaaata 2400

actgatgtgt ttgataatta gtttagtttg tggctcatgg aaactccctg taaactaaaa 2460

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<210> 226
<211> 2734
<212> DNA
<213> Homo sapien

<400> 226
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gcatccgtcc ctcaagaaga agctgcgggc acggagccag ctctctgagt tctggaaatc 180

ccataatttg gacatgatcc agttcaccga gtcctgctca atggaccaga gtgccaagga 240

acccctcatc aactacttgg atatggaata cttcggcact atctccattg gctccccacc 300

acagaacttc actgtcatct tcgacactgg ctcctccaac ctctgggtcc cctctgtgta 360

ctgcactagc ccagcctgca agacgcacag caggttccag ccttcccagt ccagcacata 420

cagccagcca ggtcaatctt tctccattca gtatggaacc gggagcttgt ccgggatcat 480

tggagccgac caagtctctg tggaaggact aaccgtggtt ggccagcagt ttggagaaag 540

tgtcacagag ccaggccaga cctttgtgga tgcagagttt gatggaattc tgggcctggg 600

ataccctcc ttggctgtgg gaggagtgac tccagtattt gacaacatga tggctcagaa 660

cctggtggac ttgccgatgt tttctgtcta catgagcagt aacccagaag gtggtgccgg 720

gagcgagctg attttcggag gctacgacca ctcccatttc tctgggagcc tgaattgggt 780

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ccaactgcct acaccctact ggacttcgtg gatggaatgc agttctgcag cagtggcttt 960

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ccttgtcttg aaaacaagat aaaacaagat aaaacctttc cctcatcaac catttgccca 2640

ggaaagaaga caattacttg gggttttgtt tcctttgttt accagttttc agaatgagtt 2700

ggtactatat taaacaccaa agaattttaa acat 2734

<210> 227
<211> 193
<212> DNA
<213> Homo sapien

<400> 227
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tttaacacgg tacaccaaca gcactcgaac tccaaaccag gcacacacga cttaacgacc 120

actggcaacg acactgcaca caggactacc acacgcagca tttacgcggg acacaccccg 180

cagccagggg cca 193

<210> 228

<211> 1457
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1024)..(1024)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (1073)..(1073)
<223> n=a, c, g or t

<400> 228
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tggcatagat tagtctccca cacaggtcaa gccagggaac cccacccagt gcctccgtcc 120

ctcgttcagg cccagcctga gtgagcccac cccagtggga ggagagggca tggccagggc 180

agggaggggg tctgagtgtc ctcctggctg ctgaaggcac cagtcagctg ccgctccagc 240

cactgcccca gtggagttct ttggttccaa gcccacagaa gaaggtggtg ggtgggccag 300

tgtgccctga ggcttcttac tggggaggga gagagtcagg tcctccactg ttaggtggcc 360

aagcgcccaa acgccatctc cactctcacc ctggatgcaa gaagtgaccc cggaggcctg 420

agtcctggcc ttggtctggt ttgatgccat ccaccgcaga ggctgttctg agggcaggtg 480

gtcagtgcag agtggcgcgc tttgtggatg gcagcctccc cccattacta ggaatctgac 540

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gcagttccgt gggaccctgc tgaacagcac gtggctgccc aacgcctgcc tggagcatcc 720

cctatcccca cccagcccaa cccatgttct cagcagcagg gatggttcta ggctggctga 780

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gaggggggctg ggcttgggct gtgctcctgt tgggtttcca ttaaccaggg gaccagctgg 900

gctgctgtga tttcactttc gcagaaaatg aaactgaagc cgtggtcacg tgacaggaca 960

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aacaataact ccacaatggc gtcggcctcg gagggtgaaa ctggagtgtg ggcaggagct 1200

gaaggaggaa gggggcccgt gcttgttccc gggctcagac agttggcaag aaaaccccga 1260

ggagccctgt tccaaagcct cctgggaccg tccaagaagg agctacatca gaggttttgg 1320

tagatgctgc tgtagacctc atatccgatg aatgggaagc tgctaatgcc atacccagca 1380

agagaaggaa gcaggatgca gccccgcttg aggccgccag cgtgccttct gcagactgtg 1440

agcagagcaa aaaaaaa 1457

<210> 229
<211> 1527
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (457)..(457)
<223> n=a, c, g or t

<400> 229
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tcaagcgggg ctgcatcctg cttccttctc ttgctgggta tggcattagc agcttcccat 180

tcatcggata tgaggtctac agcagcatct accaaaacct ctgatgtagc tccttcttgg 240

acggtccagg aggctttgga acagggctcc tcggggtttt cttgccaact gtctgagccc 300

gggaacaagc acgggccccc ttcctccttc agctcctgcc cacactccat ttcaccctcc 360

gaggccgacg ccattgtgga gttattgttc tcagaatctg ctatgggggc tgcaggaggc 420

agcctctctc cgcactggct gcagaacttg ggggttnccc cccttggaga catgctggca 480

cgaaggacac tccatgggtc ctgctgggac tgccctgcag atccagaagc aagagcagga 540

gtcgctggca gcctgctata tactacatgt cctgtcacgt gaccacggct tcagtttcat 600

tttctgcgaa agtgaaatca cagcagccca gctggtcccc tggttaatgg aaacccaaca 660

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acatgggttg ggctgggtgg ggatagggga tgctccaggc aggcgttggg cagccacgtg 840

ctgttcagca gggtcccacg gaactgccct gagcaaggcg ctcaagcctg ctgatgcctc 900

accctcctca tcctcttaag gggactaaag cacctgcccc acaggtgatg gggcctgagc 960

aggcagccca gggctactgg gctggcagtc agattcctag taatgggggg aggctgccat 1020

ccacaaagcg cgccactctg cactgaccac ctgccctcag aacagcctct gcggtggatg 1080

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ggctattcag agcaaccaca tactcag 1527

<210> 230
<211> 697
<212> DNA
<213> Homo sapien

<400> 230
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ctcgcgccga cgcgcgctac tcacactccg cctccacatg agcctccact acgccctatc 180

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caggggcgcg gcgtcgcacg gcgcgcgcgc gccgcgctcc gccccggctc gcggtcgccc 300

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tcttcccgcc ccgacgccgc cacgcgctgg ccgcgccctc ccgcgcgcgg cgcgccatag 420

ccgcctaccg ccggccctat cccgccctgc cacgcgtccg cctctctcgc gccccccctg 480

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tctgcggccc cgcgccgtca ccccgcggcc tctccacgct gtcgcccctc gccacgcccc 600

ccctcggact gtcccgcgcc ccggcccccc cgcgcccctc cctcccgccc ccccctctc 660

tccccgcgcc ctgccccctc ccctctgcct ccccccc 697

<210> 231
<211> 342
<212> DNA
<213> Homo sapien

<400> 231
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tccacgtcgt ggaaaacgct gtcgctgcca gcttgcactt aactgaatct ccggccagac 120

tgcggccagt gggaccaggg cagcgcattg cgtaataagg gcggctcttc cagccgctcc 180

actcggcctc acctgagcta cggcctcgca gcacgcggga cccgtacagc ggtgggacgc 240

gacgcgtgga ctcacgcctc agctcaaacg tgccagggaa ccacgggtca acaccaccaa 300

gacagccacg gagactaacg ggagagaaga aaaccatagc ga 342

<210> 232
<211> 250
<212> DNA
<213> Homo sapien

<400> 232
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caggaaaaac cagtgtgaga cccgaaccat gctgctgctg cccgcggggt ccctcggctc 120

ctacagctac cggagtcccc actggggcag cacctactcc gtgtcagtgg tggagaccga 180

ctacgaccag tacgcgctgc tgtacagcca aggcccaggg cttcacagag gataccattg 240

tcttcctgcc 250

<210> 233
<211> 438
<212> DNA
<213> Homo sapien

<400> 233
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tatagcctgg agtcccaggc gtgcgggcga ggtggaggac atacatttca cagatgagag 120

acaggcagat tccccacaat tctgcatgct ttggagacct gtacaatgag aagccattgg 180

tatgtcccat gctcttgctg tagtggggaa ccttgagcgt gctctgtttc aagtctcctc 240

agatcatcaa gtagtatcct gggggaaaaa cagagcgtgg tagacattga agagggagcg 300

aattgagtgt ggggatggca ttttgtgact ttgcactgag aaattcggag atacatttgt 360

catcactcca cttgtatatt ggttccggat gacgctcccc gacaagagaa taagataaat 420

aaattattgg gctgcttt 438

<210> 234
<211> 1536
<212> DNA
<213> Homo sapien

<400> 234
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gcactgcttt gttatctgtg gtggcttttc ccttggaaga tttctatctg ggcacttacc 120

atgcagttaa caacatacca aaaacagagc agcacaggct gttttatgta gcactgctga 180

ccatttgcct tggcattgga ggcgtaagag ccatcgtctg tccactgggt gcttttggcc 240

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tctgcaaact atgaattcca acctgaattt ggatggattt cttctgccga ttgcagtaat 360

gaatgccatc agcagcctac cattactaat tctggctcct tttctggagt atttcagcac 420

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attaactaaa gacttaagag cccacctgaa tgaccttgaa aatattattc catttcttgg 1140

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gataagtgca cacgttccgt taatgttgag acaacattat gtgtaaacct taaggagtgt 1500

aacccccctga aaacgaaatc cgacgaaaaa atcgtc 1536

<210> 235
<211> 351
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (274)..(274)
<223> n=a, c, g or t

<400> 235
cgcgcgaccc ggcggcggga caggcttgct gcttcctcct cctcggcctc accgtttttg 60

ccaatccaga agactgtgta gcatttggca aaggagaaaa tgccaagaag tatcttcgaa 120

cagatgacag agtagaacgt gtacgcagtt cattgtaaag ctgttacgat tagtcatatt 180

tgaacggcag agccagaatg gggctacaaa tgaagtgaaa agtatgcttt accgtgtgca 240

acaattgtga aagttaatac atacacatat gganacaatt aactaaagac ttaagagccc 300

acctgaatga cctgaaaata ttattccatt tctgggaatt ggcctcctgt a 351

<210> 236
<211> 1523
<212> DNA
<213> Homo sapien

<400> 236
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cctttttttt taccaagtct ttccctttc ccaccaagaa aacaaacccc cgtgatttct 120

ccgagccccc atattaaaca acatgggtga cccactatct gtccctccct gtgggagtaa 180

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atcacactgt ggaaacatat tatgtatgtg ccgctctaca acatctgcgc gacaacagcg 360

ggaagaggag aacctcctct tgtgggcccc actctcccag agactccaac ctataccccg 420

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<210> 237
<211> 194
<212> DNA
<213> Homo sapien

<220>
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<222> (92)..(92)
<223> n=a, c, g or t

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<222> (99)..(99)
<223> n=a, c, g or t

<220>
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<222> (160)..(160)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (168)..(168)
<223> n=a, c, g or t

<220>
<221> misc_feature
<222> (179)..(179)
<223> n=a, c, g or t

<400> 237
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tgcacaagga gcttgcccaa gctttttgtg gnggggggang aaaagtggat tgaagggagg 120

ggggcttgta aggaaagcct tgatggggcc agcccttggn attgaagnaa ccaaggtgna 180

ccccaggcca aggg 194

<210> 238
<211> 121
<212> DNA
<213> Homo sapien

<400> 238
agggcccaag tccccactac acttctcact ctcctacaaa ttattctctc atccaccaca 60

atatacaccc tacgaaccca cccataccca cgacttgcca acaaagcaca cacaattttt 120

c 121

<210> 239
<211> 1807
<212> DNA

<213> Homo sapien

<400> 239
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gatcttgcgg atgaggagga ggatcctggc ggaggaggat tgtcctagaa ttggttcccc 180

caatgggaga cgacgcaaaa gcgaggcagg agggaaaagt tcctggcctt cgggcgccaa 240

gatcccagtt cacaattatc accgggtatt taggttgctg ggaaaggaac aacacttctt 300

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tcctggggaa ggaagtgccg ctggagaaat ccttaagctg tcagccaagg tggagagctc 420

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aattttcttg gagtaattta actgaattta cacagttttg cttcattgta ttttcaaaca 600

aatagaaaat taaacttatt aggaagcatt ttcttaaagt gtttcttgct gtcttttcta 660

tctgctctaa tgttttggtc cttttattga gtttttattg cttttgatgt cagggcttat 720

ttaatctcta gtgcatgaaa gtctcatatg taaaaaatga ttattctgaa tttaatctgt 780

cattggtcat atttctaagt gttcaacctt ataaaaaaaa taaatgacta tcataaaaga 840

gaaaaacctt acattatgtt ctactagtta agttttcaag gacagtgttc actagtctac 900

catagaccct agaagagtta cccaacacat agttagcact caaatatttg tttgaatgaa 960

ttataaaaat gactacttgt actgttaatt tgtggtaatc taagggaatt aaatctcttc 1020

ggcatcattt actcccttag gtatttgact ttgtgtcaaa tgttttggca aggataaaat 1080

tataacagac tttcttgaac aaccaaaata taatctatta aggattttcc ttcacttttg 1140

ataaaataag aaaaaaggaa attaaaccct tgcatcctaa tgtaaaatag aattatatgg 1200

tgtttaatat cagtgtctaa tatagctatt atattgacct cctatagtta atacatttta 1260

tcattatttt gtatgttggt ttttaaaaat ttcataaagc tataaaaaga tacttggtca 1320

gataaagttt cctctgcttt taattttaat aaagtattat tatgtatatg atttcttttt 1380

acctattata tatatgcatc tattgttttc tcactggtaa atatgggaca gacattttgt 1440

tagaaggtta gaagtgagtt aaattttcac attcctaagg atacttttgt ctcgggttgt 1500

tgaatacatt ttaaagtgtt tataataatc acttcaaaat atttaggtaa ttaactgtaa 1560

attatgtttc ggtattctcc agggacaatg gccttagagc tattgagaat ttgatgcaaa 1620

agaaggggaa atttgattac atactgttag agaccactgg attagcagac cctggtaaga 1680

agtgagatta ttaataacca gaatatagtt ctgtgatata ttgtaaatag atgtattaga 1740

ggaatatcta aaatgagtat taaagctttt gttagtatta aaccaaaaac ttttttggt 1800

tttaaag 1807

<210> 240
<211> 376
<212> DNA
<213> Homo sapien

<400> 240
gcaaccttgt gttaggtaat agcattacca ttctgtagag gagtaaactg agacgcagca 60

agattaagtt atatgtgcaa ggataaatag ggagtaatgg aagagccgga gtttgaatct 120

gaataatcca acttcaaagt gttaatcacc actccaggct gcctctcagc cagttgaacc 180

tcataaaatt caagactata ataagtggtc aaaaacctaa gacgaaactc tgcttacatg 240

gttatttaat atttgattga caatgaaaaa taattttaat gcataaagtc atgttgaatg 300

taactacaat attaaagatc ataaagagta aagtaagtaa aatagaaaaa tcaaaataaa 360

ataaaaataa ttatgt 376

<210> 241
<211> 739
<212> DNA
<213> Homo sapien

<400> 241
ctaagatctt ttcactattg ttcctcttac acccctctcc acatggcttt gactgccttc 60

aacctttttgt agctgaatta catcatccac aaagtttgcc aaatagcccg tccagagctg 120

ctggatgacc agcaccctgt ggtccggttg ctgcgcagtt tttcctctga ctgtacaggg 180

ggccggccag tctccttgga tgccacgctg gcgcatcacc tgcaccagtg ctcctaccac 240

ctgcgcctct tccggaactg gatctgacat gagagttatg gcctctagag catgaccttc 300

ctcttgatgt tgctgctcat cttcttctac atttttgctg tgactggtgt ctacgtcttc 360

tcagagtaca cccgttcacc tcgtcaggac ctggagtacc atgtgttctt ctcgtaagca 420

gagctgggga cagctgggtg aggggagaaa atttggctaa gagaccagga agcttgtcca 480

aagtatagta atataaaaag tgcagtctat tccaagaaac tgaaatagaa cacaataggg 540

agagggaaag agaaagcaaa agaatagtga atggtattag ctctgatctt gaggttaggg 600

cagctagttc catgtttatt ctgggttttg caaattcaaa ccacactgtc atcaggcatc 660

tttaaatagc agtacactcc agtggttaag cttggtttct gtgactcagt tacctctttt 720

gaaaaatggg ggcagggcg 739

<210> 242
<211> 695

<212> DNA
<213> Homo sapien

<400> 242
tatgattcag atgaaagaga atgtcagatc agtgaaacag aataaatgaa cccagaccag 60

aatctcgtac atgcgggcag aagacaggaa gggcagaggt gtctagggca gaggtggaac 120

tagaacaaat ggtagttact tggggaaaag gtgaagttag atctgtacct tatgccaaaa 180

tgaatttcaa atgagtttaa aagttaaatg aaaaatagaa tacaacatat ttgaaagata 240

gtcactttaa atttgactgt taatatctgt attacataaa aagtcttccc aaagtcaata 300

aggaaaacat taaaaacttc aaatagcaaa aagggcagac agttcacaaa aatttctcac 360

agtaaatacg aatgactaat aaatatgggg agagggtgaa ttttggtgat ttttagcttt 420

acagatagta aaaaatgcca aaagggtgtc cttttgatct atcaaattag taaaaataaa 480

atttttactc atccttactc atcagtgcta ataacttgtg tattagcact gataaactgt 540

tggtctgtaa attggtaaaa gtgggtaaaa attgattaaa tttttcggat tataaaaaag 600

cttagatggc ggcggtggtc acaccgttaa tcccagcact tggaaggccg aagcgggtga 660

ttttcgaaat ctgactcaag tgatccactg cctga 695

<210> 243
<211> 733
<212> DNA
<213> Homo sapien

<400> 243
tgccaaaggc gtataccaaa aaaaaaagag agagagagaa aatagttgac agagagaaaa 60

tagttgagaa cagttagtag acatagtaga cgaaaaggct gttgcctgag gaagtcgcag 120

taactaagac cgtatgattc agatgaaaga gaatgtcaga tcagtgaaac agaataaatg 180

aacccagacc agaatctcgt acatgcgggc agaagacagg aagggcagag gtgtctaggg 240

cagaggtgga actagaacaa atggtagtta cttggggaaa aggtgaagtt agatctgtac 300

cttatgccaa aatgaatttc aaatgagttt aaaagttaaa tgaaaaatag aatacaacat 360

atttgaaaga tagtcacttt aaatttgact gttaatatct gtattacata aaaagtcttc 420

ccaaagtcaa taaggaaaac attgaaaact tcaaatagca aaaagggcag acagttcaca 480

aaaatttctc acagtaaata cgaatgacta ataaatatgg ggagagggtg aattttggtg 540

atttttagct ttacagatag taaaaaatgc caaaagggtg tccttttgat ctatcaaatt 600

agtaaaaata aaatttttac tcatccttac tcatcagtgc taataacttg tgtattagca 660

ctgataaact gttggtctgt aaattggtaa aagtgggtaa aaattgatta aatttttcgg 720

attataaaaa agc 733

<210> 244
<211> 684
<212> DNA
<213> Homo sapien

<400> 244
agggaaagag ggagaacaag aagagatgag agaaaagggg aaagtaaaaa agacgagaga 60

ggaagaaaaa gaaagaaaag aaagagataa gcgagacaac gcaagtcagt gcccaagagt 120

gacgacgtga acagcagacc cagaccaaac agcccaacgc cgagcagagg caggaaacgc 180

gctcacagag agccgccgga tcacgaccac accaacgaca gccaacgtgc accaccgcgg 240

aggcccctca ggagcagcac acggccgacc accgcgcagc acagcaggac aagacgccac 300

caacatcaaa caggccggcg acatagcgag agaacctgaa cacccacaac ggccagcgcg 360

cgaatcacgc gaccgcgcca gagcacacac ggcctgaggg ccacgccgcc ggccaagaca 420

gagcagggag ccacggccac acgccagcga aagacgagaa gaaacgcaag gaggagcagc 480

gccaagtagc agcccgagcg cgcacaggaa gaagcaagag cgaaacgaag cagaagccca 540

cccaccgcag gacaacaaag caagacagac agcaacagac aaatacggga ggagggaaaa 600

acagagagga gggaaagaca agcaagacag gcgacacgcg aacagacacc accaaaccgg 660

agagcgagcc ggcagagcac gaga 684

<210> 245
<211> 154
<212> DNA
<213> Homo sapien

<400> 245
agacacaccg caagacaaag acagacgcgg ccgcaccaac taacagagaa caccacacac 60

aagacaacca gccaggaaac cagccgcccc aacaggaccc ccacacacca acacccacac 120

aagacgccag accaccacga caccaaacca acca 154

<210> 246
<211> 152
<212> DNA
<213> Homo sapien

<400> 246
gttagagccg atatcactgg aagatattca aaccgtctct atgcttacga acctgcagat 60

acagctctgt tgcttgacaa catgaagaaa gctctcaagt tgctgaagac tgaattgtaa 120

atgtctgtca ggccttgaga cttgaaacca ga 152

<210> 247
<211> 968
<212> DNA

<213> Homo sapien

<400> 247
tttttttttt tttttttttt ttggtttttt tttttttttt ttaaaaaaaa aaaaataggc 60

ctcgtttata tttttctctt gtgttcaagc tgtggcattt ttgaaaaccc gtgcgtgtgt 120

ttgccaaccc tttcccccaa gaggagaatt atccgtgggg tggacccaag tctcttcagg 180

gtgtgtaaaa gggccctgtg gcccacacac agcaggactc tccagagccc tccctcatta 240

tgtggccagg aatctcaagc ctggggagtt acctcagtgg gccaataagc cgtgttccgc 300

gtggtgataa taattgtgtt atctccgctt catcaatttc ccaaccaaca ttcgcaaaca 360

caatggctcg cggactcaca aaatctcaca acaacagaca attacggaga caccaactca 420

caaaacacat aacaccaagc accgctgcaa ccgacaacga aaagccggaa atcccaagac 480

caccaaccga tccaacacag caccacacaa ccaaccacag ccacacaaca cgcaacccca 540

cccaccaccc acaaccacca ccaaaccagc acacaacaca ccaacaccca actaatcaca 600

aaacaaacaa aaaacatcac aacgcaaaac acaacaatac aacgcaacca acaccaaccc 660

cgacacccac aacaacacca caaccccacg cccagcacag cctagacaac aacaacaaaa 720

acacaaaaca aacacactca cacagacaca cccacgccac agacgcacgc cgccgccacc 780

caccccccca cacgcgaccc cgcccgcccc gacgcacaca cgccccagcc acgcacacga 840

ccgaaccccc accacgcaac ccacacagca cagcacaaac acgccccacc cagcgccaca 900

cacgcaacag accagcaccc cacacaccaa caccacacac gccctcacgc gaccgccacg 960

ccgcaccc 968

<210> 248
<211> 291
<212> DNA
<213> Homo sapien

<400> 248
gatacctgtc ccgacctctc atccccttcc cggcgaacga ccgtggccgc atttactcat 60

acgctccacc agctggtagc gctactcttc caacgctctc cgcgtagtaa tagagtgaag 120

gtcacaagat tatcacaaga gcattggggc atccgctggt cgcacccgac aaccagcaca 180

cccccggatt tcatggcacc tagtaccagg ctatgcccac actaaacata cccgagtaaa 240

tgtccattcc agtcatttcg aacatcctaa accccgcgca ccacaagaac g 291

<210> 249
<211> 28
<212> PRT
<213> Homo sapien

<400> 249

Met Phe Cys Ile Cys Phe Leu Ala Val Ser Tyr Leu Val Cys Phe Pro
1 5 10 15

Asp Leu Pro Gln Leu Phe Asn Phe Tyr Tyr Tyr Leu
20 25

<210> 250
<211> 108
<212> PRT
<213> Homo sapien

<400> 250

Met Arg Arg Trp Val Trp Ser Gln Lys Arg Tyr Arg Gln Thr Gln Ile
1 5 10 15

Leu Asn Gly Phe Ala Phe Leu Ser Met Thr Cys Ser Gln Ala Pro Gln
20 25 30

Ser Pro His Gly Leu Pro Ser Ile Trp Pro Leu Gln Pro Thr Leu Pro
35 40 45

Lys Ala Phe Cys Pro Arg Ser Pro Gly Gly Ser Pro Ala Leu Gln Ala
50 55 60

Ser His Ser Pro Met Ala Gly Gly Cys Cys Trp Ser Ala Val Lys Trp
65 70 75 80

Lys Gly Gly Pro Arg Gly Gly Leu Gly Ser Ala Pro Gly Thr Arg Ala
85 90 95

Val Ala Leu Ile Leu Thr Asn Leu Arg Arg Cys Pro
100 105

<210> 251
<211> 108
<212> PRT
<213> Homo sapien

<400> 251

Met Arg Arg Trp Val Trp Ser Gln Lys Arg Tyr Arg Gln Thr Gln Ile
1 5 10 15

Leu Asn Gly Phe Ala Phe Leu Ser Met Thr Cys Ser Gln Ala Pro Gln
20 25 30

Ser Pro His Gly Leu Pro Ser Ile Trp Pro Leu Gln Pro Thr Leu Pro
35 40 45

Lys Ala Phe Cys Pro Arg Ser Pro Gly Gly Ser Pro Ala Leu Gln Ala
50 55 60

Ser His Ser Pro Met Ala Gly Gly Cys Cys Trp Ser Ala Val Lys Trp
65 70 75 80

Lys Gly Gly Pro Arg Gly Gly Leu Gly Ser Ala Pro Gly Thr Arg Ala
85 90 95

Val Ala Leu Ile Leu Thr Asn Leu Arg Arg Cys Pro
100 105

<210> 252
<211> 71
<212> PRT
<213> Homo sapien

<400> 252

Cys Lys Ser Val Val Ala Pro Ala Thr Asp Gly Gly Leu Asn Leu Thr
1 5 10 15

Ser Thr Phe Leu Arg Lys Asn Gln Cys Glu Thr Arg Thr Met Leu Leu
20 25 30

Leu Pro Ala Gly Ser Leu Gly Ser Tyr Ser Tyr Arg Ser Pro His Trp
35 40 45

Gly Ser Thr Tyr Ser Val Ser Val Val Glu Thr Asp Tyr Asp Gln Tyr
50 55 60

Ala Leu Leu Tyr Ser Gln Gly
65 70

<210> 253
<211> 120
<212> PRT
<213> Homo sapien

<400> 253

Lys Lys Ala Ala Leu Ser Met Cys Lys Ser Val Val Ala Pro Ala Thr
1 5 10 15

Asp Gly Gly Leu Asn Leu Thr Ser Thr Phe Leu Arg Lys Asn Gln Cys
20 25 30

Glu Thr Arg Thr Met Leu Leu Gln Pro Ala Gly Ser Leu Gly Ser Tyr

35 40 45

Ser Tyr Arg Ser Pro His Trp Gly Ser Thr Tyr Ser Val Ser Val Val
50 55 60

Glu Thr Asp Tyr Asp Gln Tyr Ala Leu Leu Tyr Ala Thr Leu Tyr Ser
65 70 75 80

Arg Thr Gln Thr Pro Arg Ala Glu Leu Lys Glu Lys Phe Thr Ala Phe
85 90 95

Cys Lys Ala Gln Gly Phe Thr Glu Asp Thr Ile Val Phe Leu Pro Gln
100 105 110

Thr Asp Lys Cys Met Thr Glu Gln
115 120

<210> 254
<211> 235
<212> PRT
<213> Homo sapien

<400> 254

Ala Gly Lys Thr Thr Leu Leu Asn Tyr Ile Leu Thr Glu Gln His Ser
1 5 10 15

Lys Arg Val Ala Val Ile Leu Asn Glu Ser Gly Glu Gly Ser Ala Leu
20 25 30

Glu Lys Ser Leu Ala Val Gly Gln Gly Gly Glu Leu Tyr Glu Glu Trp
35 40 45

Leu Glu Leu Arg Asn Gly Cys Leu Cys Cys Ser Val Lys Glu Asn Gly
50 55 60

Leu Arg Ala Ile Glu Asn Leu Met Gln Lys Lys Gly Lys Phe Asp Asp
65 70 75 80

Ile Leu Leu Glu Thr Thr Gly Leu Ala Asp Pro Gly Ile Ile Thr Ile
85 90 95

Val Asp Ser Lys Tyr Trp Ile Lys Ser Glu Ile Pro Leu Lys Ala Glu
100 105 110

Glu Asn Glu Ile Ile Pro Pro Thr Asp Pro Phe Pro Ile Ala Tyr Gly
115 120 125

Gly Pro Lys Gln Gln Arg Ile Gly Gln Arg Asn Asp Ser Ser Leu Phe
130 135 140

Gly Leu Asp Thr Arg Ala Thr Asp Ile Val Leu Phe Ser Ser Thr Asn
145 150 155 160

Val Asp Ser Ile Cys Asn Arg Ser Asn Glu Ser Tyr Pro Glu Lys His
165 170 175

Leu Thr Glu Glu Lys Pro Asp Gly Leu Ile Asn Glu Ala Thr Arg Gln
180 185 190

Val Ala Leu Ala Asp Ile Ile Leu Ile Asn Lys Thr Asp Leu Val Pro
195 200 205

Glu Glu Asp Val Lys Lys Leu Arg Thr Thr Leu Arg Ser Ile Asn Gly
210 215 220

Leu Gly Gln Ile Leu Glu Thr Gln Arg Ser Arg
225 230 235

<210> 255
<211> 953
<212> PRT
<213> Homo sapien

<400> 255

Met Ser His Arg Gln Val His Asp Asp Leu Asn Lys Leu Leu Lys Ile
1 5 10 15

Met Leu Ile Asn Ser Phe Gly Ser Val Ile Ile Phe Val Phe Ile Asn
20 25 30

Ile Leu Ser Gln Phe Ser Ser Phe Ile Phe Ile Ser Glu Ile Ser Met
35 40 45

Ser Trp Asn Lys Ser Cys Val Leu Ile Ser Leu Leu Cys Asn Asn Leu
50 55 60

Val Cys Leu Thr Phe Leu Thr Phe Ile Ser Asn Ile Cys Phe Ile Lys
65 70 75 80

Asn Asn Lys His Ala Val Ile Asp Phe Ser Tyr Phe Lys Trp Met Ser
85 90 95

Glu Gln Val Thr Lys Ile Phe Cys Glu Phe Phe Ser Val Trp Cys Leu

100 105 110

Pro Met His Leu Arg Ile Trp Gly Leu Ser Glu Ile Val Leu Pro Cys
115 120 125

Tyr Gly Thr Glu Val Gly Leu Glu Ser Phe Ser Met Lys Ile Arg Cys
130 135 140

Pro Glu Tyr Glu Phe Leu Leu Leu Gly Pro Glu Ser Tyr Ile Lys Tyr
145 150 155 160

Ser Leu Lys Phe Leu Glu Ala Thr Ala Pro Ser Leu Ser Ser Val Ile
165 170 175

Phe Trp Ala Tyr Val Lys Ile Ile Thr Gln Ser Pro Val Phe Ile Asn
180 185 190

Cys Phe Phe Ile Phe Lys Pro Asn Leu Met Leu Ile Val Ile Cys Tyr
195 200 205

Leu Phe Ser Pro Asp Leu Asn His Trp Ile Gln Leu Asn Glu Phe Glu
210 215 220

Leu Ser Leu Asn Asn Ser Lys Arg Asn Asn Val Tyr Ser Asp Gly Gly
225 230 235 240

Asn Phe Leu Ser Thr Cys Ser Pro Ile Leu Asn Glu Val Lys Ser Asn
245 250 255

His Val Thr Ile Arg Val Leu Glu Lys Leu Asn Ile Leu Tyr Ile Gly
260 265 270

Tyr Leu Thr Pro His Phe Tyr Ile Thr Cys Tyr Ile Lys Gly Gly Gly
275 280 285

Ile Lys Glu Ile Gln Lys Leu Gln Arg Tyr Leu Glu Cys Thr Tyr Leu
290 295 300

Leu Ile Leu Phe Val Ile Ser Leu Phe His Leu Leu Ser Asn Lys Leu
305 310 315 320

Leu Glu Lys Phe Leu Phe Phe Ser Cys Phe Phe Ser Tyr Lys Asn Val
325 330 335

Phe Glu Lys Leu Ile Asn Phe Arg Ile Glu Lys Ile Ile Glu Ser Leu
340 345 350

Lys Lys Thr Tyr Phe Ile Glu Val Ile Thr Lys Ile Ile Phe Asn Leu
355 360 365

Asp Ser Thr Val Ile Gln Ile Leu His His Leu Pro Thr Ser Met Asn
370 375 380

Phe Met Tyr Lys Phe Phe Lys Ser Gln Ser Phe Phe Phe Leu Ile Asn
385 390 395 400

Trp Met Tyr Phe Thr Glu Phe Pro Thr Ala His Val Ser Phe Leu Pro
405 410 415

Phe Arg Val Asp Leu Ser Asn Val Leu Asp Leu His Ala Phe Asp Ser
420 425 430

Leu Ser Gly Ile Ser Leu Gln Lys Lys Leu Gln His Val Pro Gly Thr
435 440 445

Gln Pro His Leu Asp Gln Ser Ile Val Thr Ile Thr Phe Asp Val Pro
450 455 460

Gly Asn Ala Lys Glu Glu His Leu Asn Met Phe Ile Gln Asn Leu Leu
465 470 475 480

Trp Glu Lys Asn Val Arg Asn Lys Asp Asn His Cys Met Glu Val Ile
485 490 495

Arg Leu Lys Val Gln Phe Thr Val Ala Asp Phe Trp Thr Lys Ser Phe
500 505 510

Ser Trp Leu Leu Glu Lys Leu Tyr Leu Val Leu Asn Arg Asn Thr Gly
515 520 525

Phe Ser Thr Asn His Leu Cys Leu Leu Ser Phe Phe Phe Ile Ile Phe
530 535 540

Met Thr Glu Lys Glu Leu Trp Lys Ser Leu His Lys Ala Gly Phe Ile
545 550 555 560

Cys Thr Thr Phe Phe Arg Val Ala Ala Arg Thr Asn Leu Cys Ala Leu
565 570 575

Lys Cys Tyr Leu Leu Leu Ser Val Pro Lys Tyr Arg Glu Ile Met Leu
580 585 590

Gln Ile Ser Leu Leu Leu Asn Ile Met Leu Pro Asp Ala Phe Glu Gln
595 600 605

Thr Leu Asn Ile Cys Cys Thr Leu Asn Lys Val Gln Arg Thr Arg Arg
610 615 620

Ile Leu Val Leu Tyr Leu Glu Thr His Ser His Tyr Leu Ile Phe Gly
625 630 635 640

Tyr Leu Ser His Glu Arg Tyr Phe Phe Tyr Gly Ser Ser Asp Ser Gln
645 650 655

Ser Val Cys Leu Thr Ser Gln Leu Ser Val Tyr Ser Cys Val Phe Thr
660 665 670

Ser Val His Lys Val Phe Gly Glu Ile Lys Asn Ile Ile Ser Asn Glu
675 680 685

Ile Asn Phe Ile Pro Ile Gly Ala Ser Leu Ser Asp Asn Ser Phe Leu
690 695 700

Ile Ser Ala Asn Gln Tyr Thr Met Ser Ser Tyr Ser Asp Lys Tyr Asn
705 710 715 720

Ser Phe Ser Leu Phe Gln His Cys Ser Leu Ile Ala Thr His Phe Tyr
725 730 735

Asn Lys Leu Phe Asn Ile Thr Asn Ser Phe Asn Phe Ser Thr Phe Pro
740 745 750

Thr Lys Thr Val Lys His Tyr Ile Lys Ser Leu Ser Ile Gly Tyr Asp
755 760 765

Thr Tyr Phe Ile Ile Leu Phe Gln Val Leu Val Val Ile Asn Asn Thr
770 775 780

Glu Lys Pro Ser Ile Ile Tyr Val Leu Thr Leu Ser Leu Glu Lys Gly
785 790 795 800

Ile Val Gln Lys Lys Ile Asn Thr Gln Lys Pro Phe Leu Lys Ile Lys
805 810 815

Asn Ile Lys Lys Leu Leu Val Ile His Lys Tyr Leu Glu Leu Ser Asn
820 825 830

Phe Leu Ser Phe Lys Ser Leu Tyr Phe Leu Ser Glu Tyr Gln Tyr Ile
835 840 845

Asn Pro Leu Thr Leu Met Leu Ile Ser Ala Phe Lys Phe Glu Leu Arg
850 855 860

Leu Ile Asn Val Gln Ser Ile Leu Leu Gly Ala Gly Leu Val Ser Ile
865 870 875 880

Lys Asp Lys Ser Gln Gln Val Ile Val Gln Gly Val His Glu Leu Tyr
885 890 895

Asp Leu Glu Glu Thr Pro Val Ser Trp Lys Asp Asp Thr Glu Arg Thr
900 905 910

Asn Arg Leu Val Leu Ile Gly Arg Asn Leu Asp Lys Asp Ile Leu Lys
915 920 925

Gln Leu Phe Ile Ala Thr Val Thr Glu Thr Glu Lys Gln Trp Thr Thr
930 935 940

His Phe Lys Glu Asp Gln Val Cys Thr
945 950

<210> 256
<211> 728
<212> PRT
<213> Homo sapien

<400> 256

Met Arg Leu Ser Asn Arg Gln Pro Gly Ala Leu Arg Leu Thr Ala Gly
1 5 10 15

Ser Leu Val Pro Leu Ser Leu Tyr Leu Arg Asn Ser Phe Phe Gly Ser
20 25 30

Thr Ala Glu Ala Leu Gly Glu Trp Leu Cys Leu Leu Trp Gln Arg Leu
35 40 45

Glu Val Leu Thr Asp Cys His Lys Tyr Tyr Ala Val Thr Ala Ala Ala
50 55 60

Ala Tyr Met His Val Asn Ser Trp Gly Ile Asn Leu Val Cys Ile Leu
65 70 75 80

Arg Ser His Ser Ser Ala Gly Arg Gly Ser Arg Arg Met Pro Phe Ser
85 90 95

Val Ser Pro Leu Gln Pro Tyr Thr Lys Cys Ala Pro Cys Val Ser Asn
100 105 110

Ser Ile Val Glu Val Ser Asp Asn Leu Thr Tyr Thr Met Ser His Ser
115 120 125

Ser Val Ser Val Leu Phe Leu Leu Val Phe Tyr Asn Ser Phe Leu Leu
130 135 140

Asn Phe Ser Pro Leu Tyr Lys Met Ser His Arg Gln Val His Asp Thr
145 150 155 160

Tyr Asn Lys Leu Leu Lys Ile Met Leu Ile Asn Ser Phe Gly Ser Val
165 170 175

Ile Ile Phe Val Phe Ile Asn Ile Leu Ser Gln Phe Ser Ser Phe Ile
180 185 190

Phe Ile Ser Glu Ile Ser Met Ser Trp Asn Lys Ser Cys Val Leu Ile
195 200 205

Ser Leu Leu Cys Asn Asn Leu Val Cys Leu Thr Phe Leu Thr Phe Ile
210 215 220

Ser Asn Ile Cys Phe Ile Ile Glu Gln Lys His Ala Val Ile Asp Phe
225 230 235 240

Ser Tyr Phe Lys Trp Met Ser Glu Gln Val Thr Lys Ile Phe Cys Glu
245 250 255

Phe Phe Ser Val Trp Cys Leu Pro Met His Leu Arg Ile Gln Gly Leu
260 265 270

Ser Glu Ile Val Leu Pro Cys Tyr Gly Thr Glu Val Gly Leu Glu Ser
275 280 285

Phe Ser Met Lys Ile Arg Cys Pro Glu Tyr Glu Phe Leu Leu Leu Gly
290 295 300

Pro Glu Ser Tyr Ile Lys Tyr Ser Leu Lys Phe Leu Glu Ala Thr Ala
305 310 315 320

Pro Ser Leu Ser Ser Val Ile Phe Trp Ala Tyr Val Lys Ile Ile Thr
325 330 335

Gln Ser Pro Val Phe Ile Asn Cys Phe Phe Ile Phe Lys Pro Asn Leu
340 345 350

Met Leu Ile Val Ile Cys Tyr Leu Phe Ser Pro Asp Leu Asn His Trp
355 360 365

Ile Gln Leu Asn Glu Phe Glu Leu Ser Leu Asn Asn Ser Lys Arg Asn
370 375 380

Asn Val Tyr Ser Asp Gly Gly Asn Phe Leu Ser Thr Cys Ser Pro Ile
385 390 395 400

Leu Asn Glu Val Lys Ser Asn His Val Thr Ile Arg Val Leu Glu Lys
405 410 415

Leu Asn Ile Leu Tyr Ile Gly Tyr Leu Thr Pro His Phe Tyr Ile Thr
420 425 430

Cys Tyr Ile Lys Gly Gly Gly Ile Lys Glu Ile Gln Lys Leu Gln Arg
435 440 445

Tyr Leu Glu Cys Thr Tyr Leu Leu Ile Leu Phe Val Ile Ser Leu Phe
450 455 460

His Leu Leu Ser Asn Lys Leu Leu Glu Lys Phe Leu Phe Phe Ser Cys
465 470 475 480

Phe Phe Ser Tyr Lys Asn Val Phe Glu Lys Leu Ile Asn Phe Arg Ile
485 490 495

Glu Lys Ile Ile Glu Ser Leu Lys Lys Thr Tyr Phe Ile Glu Val Ile
500 505 510

Thr Lys Ile Ile Phe Asn Leu Asp Ser Thr Val Ile Gln Ile Leu His
515 520 525

His Leu Pro Thr Ser Met Asn Phe Met Tyr Lys Ile Phe Lys Ser Gln
530 535 540

Ser Phe Phe Phe Leu Ile Asn Trp Met Tyr Phe Thr Glu Phe Pro Thr
545 550 555 560

Ala His Val Ser Phe Leu Pro Phe Arg Val Asp Leu Ser Asn Val Leu
565 570 575

Asp Leu His Ala Phe Asp Ser Leu Ser Gly Ile Ser Leu Gln Lys Lys
580 585 590

Leu Gln His Val Pro Gly Thr Gln Pro His Leu Asp Gln Ser Ile Val
595 600 605

Thr Ile Thr Phe Asp Val Pro Gly Asn Ala Lys Glu Glu His Leu Asn
610 615 620

Met Phe Ile Gln Asn Leu Leu Trp Glu Lys Asn Val Arg Asn Lys Asp
625 630 635 640

Asn His Cys Met Glu Val Ile Arg Leu Lys Gly Leu Val Ser Ile Lys
645 650 655

Asp Lys Ser Gln Gln Val Ile Val Gln Gly Val His Glu Leu Tyr Asp
660 665 670

Leu Glu Glu Thr Pro Val Ser Trp Lys Asp Asp Thr Glu Arg Thr Asn
675 680 685

Arg Leu Val Leu Ile Gly Arg Asn Leu Asp Lys Asp Ile Leu Lys Gln
690 695 700

Leu Phe Ile Ala Thr Val Thr Glu Thr Glu Lys Gln Trp Thr Thr His
705 710 715 720

Phe Lys Glu Asp Gln Val Cys Thr
725

<210> 257
<211> 151
<212> PRT
<213> Homo sapien

<400> 257

Met Gly Gly Gly Cys His Pro Gln Ser Ala Pro Leu Cys Thr Asp His
1 5 10 15

Leu Pro Ser Glu Gln Pro Leu Arg Trp Met Ala Ser Asn Gln Thr Lys
20 25 30

Ala Arg Thr Gln Ala Ser Gly Val Thr Ser Cys Ile Gln Gly Glu Ser
35 40 45

Gly Asp Gly Val Trp Ala Leu Gly His Leu Thr Val Glu Asp Leu Thr
50 55 60

Leu Ser Leu Pro Ser Lys Lys Pro Gln Gly Thr Leu Ala His Pro Pro
65 70 75 80

Pro Ser Ser Val Gly Leu Glu Pro Lys Asn Ser Thr Gly Ala Val Ala
85 90 95

Gly Ala Ala Ala Asp Trp Cys Leu Gln Gln Pro Gly Gly His Ser Asp
100 105 110

Pro Leu Pro Ala Leu Ala Met Pro Ser Pro Pro Thr Gly Val Gly Ser
115 120 125

Leu Arg Leu Gly Leu Asn Glu Gly Arg Arg His Trp Val Gly Phe Pro
130 135 140

Gly Leu Thr Cys Val Gly Asp
145 150

<210> 258
<211> 72
<212> PRT
<213> Homo sapien

<400> 258

Met Ala Ser Ala Ser Glu Gly Glu Met Glu Cys Gly Gln Glu Leu Lys
1 5 10 15

Glu Glu Gly Gly Pro Cys Leu Phe Pro Gly Ser Asp Ser Trp Gln Glu
20 25 30

Asn Pro Glu Glu Pro Cys Ser Lys Ala Ser Trp Thr Val Gln Glu Val
35 40 45

Ser Ala Leu Pro Arg Leu Pro Ser Ala Pro Ala His Ser Ala Gln Glu
50 55 60

Asn Leu Thr Ala Gln Leu Pro Ser
65 70

<210> 259
<211> 119
<212> PRT
<213> Homo sapien

<400> 259

Asn Gly Arg Ser Val Leu Glu Ser Ala Phe Glu Arg Arg Pro Gly Arg

250

1 5 10 15

Tyr Lys Ala Asp Leu Ser Pro Glu Asn Ala Lys Leu Leu Ser Thr Phe
20 25 30

Leu Asn Gln Thr Gly Leu Asp Ala Phe Leu Leu Glu Leu His Glu Met
35 40 45

Ile Ile Leu Lys Leu Lys Asn Pro Gln Thr Gln Thr Glu Glu Arg Phe
50 55 60

Arg Pro Gln Trp Ser Leu Arg Asp Thr Leu Val Ser Tyr Met Gln Thr
65 70 75 80

Lys Glu Ser Glu Ile Leu Pro Glu Met Ala Ser Gln Phe Pro Glu Glu
85 90 95

Ile Leu Leu Ala Ser Cys Val Ser Val Trp Lys Thr Ala Ala Val Leu
100 105 110

Lys Trp Asn Arg Glu Met Arg
115

<210> 260
<211> 127
<212> PRT
<213> Homo sapien

<400> 260

Met Val Leu Gly Arg Leu Leu Phe Leu Leu Ser Leu Leu Asp Trp His
1 5 10 15

Gln Tyr Tyr Asp Ile Val Tyr Met Lys Pro His Gly Arg Leu Gln Lys
20 25 30

Val Met Asn His Ile Thr Asp Gly Pro Arg Lys Asp Leu Val Lys Gly
35 40 45

Lys Gln Ile Ala Ala Ala Leu Met Leu Asp Ser Thr Phe Ser Ile Leu
50 55 60

Gln Thr Trp Asp Thr Ile Asn Leu Asn Ser Phe Phe Thr Gln Phe Glu
65 70 75 80

Gln Phe Cys Phe Val Leu Gln Gln Pro Met Ile Tyr Glu Gly Gln Ala
85 90 95

Gln Leu Trp Thr Asp Leu Gln Tyr Arg Glu Lys Glu Val Ser Gly Leu
100 105 110

Pro Pro Ala Ala Leu Pro Ala Gly Gln Glu Pro His Leu Thr Cys
115 120 125

<210> 261
<211> 130
<212> PRT
<213> Homo sapien

<400> 261

Ser Val Leu Lys Pro Gly Lys Arg Gly Glu Lys Ala Leu Gln Arg Ala
1 5 10 15

Glu Arg Glu Ala Asp His Arg Arg Glu Lys Gly Lys Ile Leu Ala Pro
20 25 30

Thr Val Ala Arg Val Leu Ser Phe Cys Pro His Glu Cys Asp Ser Ala
35 40 45

Arg Asn Leu Glu Trp Leu Lys Thr Val Asn Glu Ser His Gly Ser Val
50 55 60

Glu Arg Ser Ser Leu Thr Leu Ala Thr Ala Ile Asn Gln Arg Gly Ile
65 70 75 80

Tyr Val Ile Gln Ala Pro Lys Gly Gly Gln Lys Ile Ser Pro Asp Thr
85 90 95

Val Leu His Leu Ile Leu Pro Glu Ser Pro Gly Ser His Glu Glu Ser
100 105 110

Arg Glu Tyr Ser Leu Glu Lys Val Ser Arg Val Ser Lys Gln Asn Pro
115 120 125

Leu Leu
130

<210> 262
<211> 160
<212> PRT
<213> Homo sapien

<400> 262

Met Thr Asn Thr Lys Gly Lys Arg Arg Cys Thr Gln Tyr Met Ser Ser
1 5 10 15

Arg Pro Phe Arg Lys Tyr Gly Val Val Pro Leu Ala Thr Trp Tyr Met
20 25 30

Arg Ile Tyr Glu Thr Gly Asp Thr Val Asp Ile Lys Gly Met Gly Thr
35 40 45

Val Gln Lys Gly Met Ser His Lys Cys Tyr His Gly Lys Thr Gly Arg
50 55 60

Val Tyr Gly Ile Thr Gln Arg Ala Val Gly Ile Val Val Asn Lys Gln
65 70 75 80

Val Thr Gly Gln Ile Leu Ala Lys Arg Ile Val Pro Ile Glu His Ile
85 90 95

Lys His Thr Lys Ser Gln Asp Ser Phe Leu Lys Cys Val Lys Glu Asn
100 105 110

Asp Gln Lys Lys Lys Glu Ala Lys Glu Lys Gly Thr Trp Val Gln Ile
115 120 125

Lys Arg Gln Pro Ala Pro Pro Arg Glu Ala Tyr Phe Val Arg Thr Ser
130 135 140

Gly Lys Glu Pro Glu Leu Leu Glu Pro Ile Pro Tyr Glu Phe Met Ala
145 150 155 160

<210> 263
<211> 194
<212> PRT
<213> Homo sapien

<400> 263

Trp Arg Glu Phe Thr Gly Asn Arg Leu Gln Gln Leu Arg Leu Leu Pro
1 5 10 15

Thr Gly Ser Tyr Thr Val Cys Phe Ser Gly Cys Ser Arg Leu Ala Leu
20 25 30

Asn Leu Asn Pro Gly Thr Phe Leu Ser Gly Phe Leu Leu Leu Leu Asn
35 40 45

Ile Phe Leu His Thr Phe Gln Glu Ala Leu Leu Ala Leu Ser Val Leu
50 55 60

Asn Val Leu Asn Arg His Asn Ser Leu Gly Lys Asn Leu Ala Cys Asn
65 70 75 80

Leu Phe Val Tyr Asn Asn Ala Asn Ser Thr Leu Gly Asn Thr Val Asp
85 90 95

Ser Ser Ser Phe Ala Met Val Thr Phe Val Gly His Ser Phe Leu Asn
100 105 110

Ser Thr His Ser Leu Asp Val Tyr Ser Ile Thr Cys Leu Ile Asp Ser
115 120 125

His Val Pro Cys Gly Gln Arg Asn Asn Ser Ile Phe Ser Lys Arg Pro
130 135 140

Arg Gly His Ile Leu Gly Ala Ser Pro Leu Ser Leu Cys Ile Cys His
145 150 155 160

Phe Gly Lys Leu Leu Glu Asp Gly Cys Ser Ser Gln Lys Val Leu Ser
165 170 175

Leu Leu Lys Cys Phe Phe Leu Tyr Leu Glu Cys Leu Val Ser Arg Ile
180 185 190

Ser Phe

<210> 264
<211> 71
<212> PRT
<213> Homo sapien

<400> 264

Met Ala Arg Tyr Glu Glu Val Ser Val Ser Gly Phe Glu Glu Phe His
1 5 10 15

Arg Ala Val Glu Gln His Asn Cys Trp Lys Asp Pro Asn Asn Asp Phe
20 25 30

Arg Lys Asn Leu Lys Val Thr Ala Val Pro Thr Leu Leu Lys Tyr Gly
35 40 45

Thr Pro Gln Lys Leu Val Glu Ser Glu Cys Leu Gln Ala Asn Leu Val
50 55 60

Glu Met Leu Phe Ser Glu Asp
65 70

<210> 265
<211> 243
<212> PRT
<213> Homo sapien

<400> 265

Gln Thr Leu Pro Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp
1 5 10 15

Met Asp Asp Glu Asp Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile
20 25 30

Asp Ser Asn Asp Ser Asp Asp Val Asp Asp Thr Asp Asp Ser His Gln
35 40 45

Ser Asp Glu Ser His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp
50 55 60

Phe Pro Thr Asp Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro
65 70 75 80

Thr Val Asp Thr Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu
85 90 95

Arg Ser Lys Ser Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp
100 105 110

Ala Thr Asp Glu Asp Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn
115 120 125

Gly Ala Tyr Lys Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser
130 135 140

Asp Trp Asp Ser Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp
145 150 155 160

Asp Gln Ser Ala Glu Thr His Ser His Arg Gln Ser Arg Leu Tyr Lys
165 170 175

Arg Lys Ala Asn Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser
180 185 190

Gln Glu Leu Ser Lys Val Ser Arg Glu Phe His Ser His Glu Phe His
195 200 205

Ser His Glu Asp Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp
210 215 220

Lys His Leu Lys Phe Arg Ile Ser His Glu Leu Asp Ser Ala Ser Ser
225 230 235 240

Glu Val Asn

<210> 266
<211> 62
<212> PRT
<213> Homo sapien

<400> 266

Met Leu Gly Val Lys Phe Tyr Val Pro Ser Leu Leu Glu Phe Lys Ile
1 5 10 15

Tyr Asn Leu Phe Phe Cys Met Leu Thr Phe Leu Lys Arg Ile His Leu
20 25 30

Leu Ser Gln Ile Ser Lys Ser Lys Glu Arg Lys Ile Ile Ser Tyr Tyr
35 40 45

Gln Lys Ala Leu Gly Phe Leu Met Gln Asn Asn Pro Ser Asn
50 55 60

<210> 267
<211> 305
<212> PRT
<213> Homo sapien

<400> 267

Gln Phe Leu Gly Arg Trp Phe Ser Ala Gly Leu Ala Ser Asn Ser Ser
1 5 10 15

Trp Leu Arg Glu Lys Lys Ala Ala Leu Ser Met Cys Lys Ser Val Val
20 25 30

Ala Pro Ala Thr Asp Gly Gly Leu Asn Leu Thr Ser Thr Phe Leu Arg
35 40 45

Lys Asn Gln Cys Glu Thr Arg Thr Met Leu Leu Gln Pro Ala Gly Ser
50 55 60

Leu Gly Ser Tyr Ser Tyr Arg Ser Pro Arg Glu Trp Gly Leu His Arg
65 70 75 80

Pro Pro Gly Pro Ser Leu Gly Ala Thr Leu Ala Gly Thr Thr Leu Gly
85 90 95

Gln Pro Pro Ala Ala Glu Ile His Gly Val Gly Gly Asp Gly Cys Pro
100 105 110

Thr Ser Val Arg Gly Lys Gly Gln Arg Thr Gln Gly Phe Pro His Ser
115 120 125

His Leu Gly Asn Gly Ser His Gly Glu Thr Ser Ser Leu Pro Val Leu
130 135 140

Ala Ala Thr Ser Ala Ala Ala Pro Gly Ile Leu Val Phe Ala Trp Leu
145 150 155 160

Pro Gln Ile Leu Val Trp Gly Gln Gly Ser Gln Ala Val Gln Ala Arg
165 170 175

Ala Gly His Trp Leu Glu Ser Ser Arg Val Gly Glu His Pro Gly Pro
180 185 190

Ala Glu Gly Leu Ser Ala Pro Lys Ala His Arg Cys Thr Pro Ser Leu
195 200 205

Lys Gln Arg Gly Leu Gly Gly Val Pro Asp Arg Val Val Ser Trp Val
210 215 220

Pro Arg Leu Gly Ser Thr Tyr Ser Val Ser Val Val Glu Thr Asp Tyr
225 230 235 240

Asp Gln Tyr Ala Leu Leu Tyr Ser Gln Gly Ser Lys Gly Pro Gly Glu
245 250 255

Asp Phe Arg Met Ala Thr Leu Tyr Ser Arg Thr Gln Thr Pro Arg Ala
260 265 270

Glu Leu Lys Glu Lys Phe Thr Ala Phe Cys Lys Ala Gln Gly Phe Thr
275 280 285

Glu Asp Thr Ile Val Phe Leu Pro Gln Thr Asp Lys Cys Met Thr Glu
290 295 300

Gln
305

<210> 268
<211> 262
<212> PRT
<213> Homo sapien

<400> 268

Arg Arg His Ser Ser Arg Ser Ser Cys Ser Gly Pro Pro Arg Pro Gly
1 5 10 15

His Leu Pro Arg Ser Pro Thr Pro Leu Ala Pro Gly Pro Gly His Pro
20 25 30

Leu Cys Cys Arg Arg Met Ala Thr His His Thr Leu Trp Met Gly Leu
35 40 45

Ala Leu Leu Gly Val Leu Gly Asp Leu Gln Ala Ala Pro Glu Ala Gln
50 55 60

Val Ser Val Gln Pro Asn Phe Gln Gln Asp Lys Phe Leu Gly Arg Trp
65 70 75 80

Phe Ser Ala Gly Leu Ala Ser Asn Ser Ser Trp Leu Arg Glu Lys Lys
85 90 95

Ala Ala Leu Ser Met Cys Lys Ser Val Val Ala Pro Ala Thr Asp Gly
100 105 110

Gly Leu Asn Leu Thr Ser Thr Phe Leu Arg Lys Asn Gln Cys Glu Thr
115 120 125

Arg Thr Met Leu Leu Gln Pro Ala Gly Ser Leu Gly Ser Tyr Ser Tyr
130 135 140

Arg Ser Pro Arg Glu Trp Gly Leu His Arg Pro Pro Gly Pro Ser Leu
145 150 155 160

Gly Ala Thr Leu Ala Gly Thr Thr Leu Gly Gln Pro Pro Ala Ala Glu
165 170 175

Ile His Gly Val Gly Gly Asp Trp Gly Ser Thr Tyr Ser Val Ser Val
180 185 190

Val Glu Thr Asp Tyr Asp Gln Tyr Ala Leu Leu Tyr Ser Gln Gly Ser
195 200 205

Lys Gly Pro Gly Glu Asp Phe Arg Met Ala Thr Leu Tyr Ser Arg Thr
210 215 220

Gln Thr Pro Arg Ala Glu Leu Lys Glu Lys Phe Thr Ala Phe Cys Lys
225 230 235 240

Ala Gln Gly Phe Thr Glu Asp Thr Ile Val Phe Leu Pro Gln Thr Asp
245 250 255

Lys Cys Met Thr Glu Gln
260

<210> 269
<211> 450
<212> PRT
<213> Homo sapien

<400> 269

Arg Arg His Ser Ser Arg Ser Ser Cys Ser Gly Pro Pro Arg Pro Gly
1 5 10 15

His Leu Pro Arg Ser Pro Thr Pro Leu Ala Pro Gly Pro Gly His Pro
20 25 30

Leu Cys Cys Arg Arg Met Ala Thr His His Thr Leu Trp Met Gly Leu
35 40 45

Ala Leu Leu Gly Val Leu Gly Asp Leu Gln Ala Ala Pro Glu Ala Gln
50 55 60

Val Ser Val Gln Pro Asn Phe Gln Gln Asp Lys Val Arg Gly Phe Pro
65 70 75 80

Ala Ser Ser Pro Arg Ala Thr Gly Pro Cys Gln Gly Lys Gly Thr Phe
85 90 95

Arg Leu Gly Leu Pro Pro Gly Arg Ser Glu Arg Ser Pro Ala Val Pro
100 105 110

Gly Ser Ala Gly Gln Gly Leu Ser Gly Arg Ala Gly Arg Arg Leu Gly
115 120 125

Ser Arg Pro Arg Arg Leu Pro Ala Arg Ala Leu Pro Gly His Arg Val
130 135 140

Pro Ser Pro Leu Met Gly His Ala Asp Thr Gly Pro His Thr Arg Pro
145 150 155 160

Arg Gln Pro Asp Thr Ser Thr Pro Val Gly Thr Arg Pro Pro Glu Asp
165 170 175

Thr Arg Ala His Val Pro His Leu Gly Ala Arg Thr Arg Ala Gly Gly
180 185 190

Ala Gln Gly Trp Arg Gln Thr Leu Arg Ala Arg Trp Gly Leu Gly Gly
195 200 205

Thr Arg Thr Ala Gln Thr Ala Gly Asp Ala Arg Ser Arg Pro Gly Ala
210 215 220

Ala Arg Gly Ser Ala Gly Ala Arg Val Pro Ala Pro Arg Ala Pro Pro
225 230 235 240

Trp Arg Arg Gly Glu Pro Gln Arg Ser Ala Glu Leu Ser Arg Arg Pro
245 250 255

Ala Pro Ile Pro Ala Arg Asn Ala Thr Ser Ser Ala Ala Arg Cys Met
260 265 270

Gly Gln Ala Leu Ser Gln Gly Thr Glu Ser Gly Pro Gly Ala Glu Gly
275 280 285

Pro Lys Leu Ala Gly Gly Arg Arg Ala Arg Phe Leu Gly Arg Trp Phe
290 295 300

Ser Ala Gly Leu Ala Ser Asn Ser Ser Trp Leu Arg Glu Lys Lys Ala
305 310 315 320

Ala Leu Ser Met Cys Lys Ser Val Val Ala Pro Ala Thr Asp Gly Gly
325 330 335

Leu Asn Leu Thr Ser Thr Phe Leu Arg Lys Asn Gln Cys Glu Thr Arg
340 345 350

Thr Met Leu Leu Gln Pro Ala Gly Ser Leu Gly Ser Tyr Ser Tyr Arg
355 360 365

Ser Pro His Trp Gly Ser Thr Tyr Ser Val Ser Val Val Glu Thr Asp
370 375 380

Tyr Asp Gln Tyr Ala Leu Leu Tyr Ser Gln Gly Ser Lys Gly Pro Gly
385 390 395 400

Glu Asp Phe Arg Met Ala Thr Leu Tyr Ser Arg Thr Gln Thr Pro Arg

405 410 415

Ala Glu Leu Lys Glu Lys Phe Thr Ala Phe Cys Lys Ala Gln Gly Phe
420 425 430

Thr Glu Asp Thr Ile Val Phe Leu Pro Gln Thr Asp Lys Cys Met Thr
435 440 445

Glu Gln
450

<210> 270
<211> 447
<212> PRT
<213> Homo sapien

<400> 270

Arg Arg His Ser Ser Arg Ser Ser Cys Ser Gly Pro Pro Arg Pro Gly
1 5 10 15

His Leu Pro Arg Ser Pro Thr Pro Leu Ala Pro Gly Pro Gly His Pro
20 25 30

Leu Cys Cys Arg Arg Met Ala Thr His His Thr Leu Trp Met Gly Leu
35 40 45

Ala Leu Leu Gly Val Leu Gly Asp Leu Gln Ala Ala Pro Glu Ala Gln
50 55 60

Val Ser Val Gln Pro Asn Phe Gln Gln Asp Lys Val Arg Gly Phe Pro
65 70 75 80

Ala Ser Ser Pro Arg Ala Thr Gly Pro Cys Gln Gly Lys Gly Thr Phe
85 90 95

Arg Leu Gly Leu Pro Pro Gly Arg Ser Glu Arg Ser Pro Ala Val Pro
100 105 110

Gly Ser Ala Gly Gln Gly Leu Ser Gly Arg Ala Gly Arg Arg Leu Gly
115 120 125

Ser Arg Pro Arg Arg Leu Pro Ala Arg Ser Pro Pro Trp Ala Pro Arg
130 135 140

Pro Val Ser Pro Asp Gly Pro Arg Arg His Arg Ala Thr His Ala Pro
145 150 155 160

Thr Pro Ala Arg His Val His Pro Cys Gly His Ala Thr Pro Arg Gly
165 170 175

His Thr Ser Ala Arg Ser Thr Pro Gly Cys Gln Asp Thr Gly Gly Trp
180 185 190

Gly Thr Gly Met Ala Thr Asn Thr Pro Cys Ala Val Gly Val Gly Arg
195 200 205

Asp Ala His Arg Thr Asp Ser Arg Arg Arg Ala Leu Ser Pro Gly Ser
210 215 220

Cys Ser Gly Lys Arg Arg Ser Ala Gly Pro Arg Ala Ala Arg Pro Ser
225 230 235 240

Leu Ala Ser Arg Arg Thr Pro Ala Val Arg Arg Ala Glu Pro Lys Thr
245 250 255

Arg Pro Asp Pro Arg Gln Glu Cys Asp Val Leu Cys Arg Pro Leu Tyr
260 265 270

Gly Pro Gly Ala Gln Pro Gly His Arg Ile Gly Thr Gly Gly Gly Gly
275 280 285

Ala Glu Ala Gly Trp Trp Ala Ala Cys Glu Gly Glu Gly Leu Ser Ser
290 295 300

Gly Gly Ala Trp Pro Asp Gly Gly Ala Gly Cys Gln Gly Arg Gly Gln
305 310 315 320

Leu Leu Gly Arg Arg Cys Glu Gly Arg Gly His Leu Leu Gly Arg Gly
325 330 335

Leu Arg Gly Gly Gly Gln Phe Leu Gly Arg Gly Val Arg Gly Val Ala
340 345 350

Ala Arg Gly Ile Gly Arg Gly Gly Gly Ala Gly Leu Glu Thr Gly Gly
355 360 365

Val Asp Gly Arg Gly Ala Pro Ala Gly Arg Arg Arg Trp Val Arg Arg
370 375 380

Val Leu Ala Asp Ala Gly Gly Gly Arg Ser Pro Gln Phe Pro Gly Ala
385 390 395 400

Leu Val Gln Arg Gly Pro Arg Leu Gln Leu Glu Leu Ala Pro Gly Glu
405 410 415

Glu Gly Gly Val Val His Val Gln Val Cys Gly Gly Pro Cys His Gly
420 425 430

Trp Trp Pro Gln Pro Asp Leu His Leu Pro Gln Glu Lys Pro Val
435 440 445

<210> 271
<211> 135
<212> PRT
<213> Homo sapien

<400> 271

Met Ala Ala Gly Pro Met Ala Ala Glu Pro Cys Gly Pro His Ala Leu
1 5 10 15

Val Ala Leu Ala Gly Leu Val Thr Gly Ile Pro Thr His His Pro Arg
20 25 30

Val Tyr Asn Ile His Ser Arg Thr Val Thr Arg Tyr Pro Ala Asn Ser
35 40 45

Ile Val Val Val Gly Gly Cys Pro Val Cys Arg Val Gly Val Leu Glu
50 55 60

Asp Cys Phe Thr Phe Leu Gly Ile Phe Leu Ala Ile Ile Leu Phe Arg
65 70 75 80

Ile Gly Pro Ala Ala Ile Gly Gln Trp Gln Pro Pro Asn Gly Ser Arg
85 90 95

Thr Gln Thr Pro Arg Ala Glu Leu Lys Glu Lys Phe Thr Ala Phe Cys
100 105 110

Lys Ala Gln Gly Phe Thr Glu Asp Thr Ile Val Phe Leu Pro Gln Thr
115 120 125

Asp Lys Cys Met Thr Glu Gln
130 135

<210> 272
<211> 150
<212> PRT
<213> Homo sapien

<400> 272

Ala Leu Leu Glu Ala Trp Ala Arg Asp Arg Gly Val Ser Val Gln Val
1 5 10 15

Arg Thr Ser Leu Pro Gln Pro Leu His Glu Glu Pro Pro Pro Trp Gly
20 25 30

Thr Trp Arg Pro Gly Ala His Ser Val Pro Gly Pro Ser Ser Ser Gln
35 40 45

Asp Val Gly Leu Gln Pro Gly Gly Gly His Arg Val Glu Gly Ala His
50 55 60

Gly Gly Tyr Arg Gly Thr Asn His Thr Gly Leu Arg His Ser Leu Leu
65 70 75 80

Gly Val Asp Ser Leu Leu Leu Ala Glu Val Glu Lys Asp Pro Leu Phe
85 90 95

Val Ser Ser Ala Gln Gly Glu Val Gly Gly Asp Gly Gly Ser Val Gln
100 105 110

Phe Gly Gly Ser Val Lys Thr Ser Ser Ala Leu Arg Glu Glu Gln Glu
115 120 125

Ala Gln Trp Glu Asn Trp Pro Lys Ser Gly Val Leu Thr Thr Ala Pro
130 135 140

Gly Phe Phe Leu Gly Arg
145 150

<210> 273
<211> 227
<212> PRT
<213> Homo sapien

<400> 273

Arg Arg His Ser Ser Arg Ser Ser Cys Ser Gly Pro Pro Arg Pro Gly
1 5 10 15

His Leu Pro Arg Ser Pro Thr Pro Leu Ala Pro Gly Pro Gly His Pro
20 25 30

Leu Cys Cys Arg Arg Met Ala Thr His His Thr Leu Trp Met Gly Leu
35 40 45

Ala Leu Leu Gly Val Leu Gly Asp Leu Gln Ala Ala Pro Glu Ala Gln

50 55 60

Val Ser Val Gln Pro Asn Phe Gln Gln Asp Lys Phe Leu Gly Arg Trp
65 70 75 80

Phe Ser Ala Gly Leu Ala Ser Asn Ser Ser Trp Leu Arg Glu Lys Lys
85 90 95

Ala Ala Leu Ser Met Cys Lys Ser Val Val Ala Pro Ala Thr Asp Gly
100 105 110

Gly Leu Asn Leu Thr Ser Thr Phe Leu Arg Lys Asn Gln Cys Glu Thr
115 120 125

Arg Thr Met Leu Leu Gln Pro Ala Gly Ser Leu Gly Ser Tyr Ser Tyr
130 135 140

Arg Ser Pro His Trp Gly Ser Thr Tyr Ser Val Ser Val Val Glu Thr
145 150 155 160

Asp Tyr Asp Gln Tyr Ala Leu Leu Tyr Ser Gln Gly Ser Lys Gly Pro
165 170 175

Gly Glu Asp Phe Arg Met Ala Thr Leu Tyr Ser Arg Thr Gln Thr Pro
180 185 190

Arg Ala Glu Leu Lys Glu Lys Phe Thr Ala Phe Cys Lys Ala Gln Gly
195 200 205

Phe Thr Glu Asp Thr Ile Val Phe Leu Pro Gln Thr Asp Lys Cys Met
210 215 220

Thr Glu His
225

<210> 274
<211> 122
<212> PRT
<213> Homo sapien

<400> 274

Arg Arg Ser Val Met Asp Trp Ser Arg Pro Arg Tyr Pro Asp Ala Thr
1 5 10 15

Asp Glu Asp Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala
20 25 30

Tyr Lys Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp
35 40 45

Asp Ser Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln
50 55 60

Ser Ala Glu Thr His Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys
65 70 75 80

Ala Asn Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu
85 90 95

Leu Ser Lys Val Ser Arg Glu Phe His Ser His Glu Phe His Ser His
100 105 110

Glu Asp Met Leu Val Val Asp Pro Gln Lys
115 120

<210> 275
<211> 63
<212> PRT
<213> Homo sapien

<400> 275

Val Ile Asp Val Ile His Glu Val Ala His Ser Trp Phe Gly Asn Ala
1 5 10 15

Val Thr Asn Ala Thr Trp Glu Glu Met Trp Leu Ser Glu Gly Leu Ala
20 25 30

Thr Tyr Ala Gln Arg Arg Ile Thr Thr Glu Thr Tyr Gly Ala Ala Phe
35 40 45

Thr Cys Leu Glu Thr Ala Phe Arg Leu Asp Ala Leu His Arg Gln
50 55 60

<210> 276
<211> 116
<212> PRT
<213> Homo sapien

<400> 276

Met Leu Trp Val Trp Phe His Ile Thr Ala Ile Lys Leu Gln Arg Glu
1 5 10 15

Glu Glu Glu Ala Phe Ala Ser Ser Gln Ser Ser Gln Gly Ala Gln Ser
20 25 30

Leu Ile Phe Ser Lys Phe Glu Gly Lys Lys Thr Asn Lys Lys Thr Arg
35 40 45

Lys Val Thr Thr Val Lys Lys Ser Ser Val Arg Leu Pro Gly Ser Asp
50 55 60

Gln Arg Arg Ile Leu Lys Trp Ile Pro Gly Val Cys Leu Glu Thr Ser
65 70 75 80

Trp Pro Ala Ser Pro Ser Ala Ala Ser Thr Ser Ser Met Pro Ser Arg
85 90 95

Ser Pro Arg Thr Ser Trp Arg Gln Gln Met Thr Ser Ser Pro Pro Ser
100 105 110

Ser Thr Leu Phe
115

<210> 277
<211> 57
<212> PRT
<213> Homo sapien

<400> 277

Met Asp Arg Val Ser Lys Glu Phe Ile Glu Phe Leu Lys Thr Phe Cys
1 5 10 15

Lys Thr Gly Gln Glu Ile Tyr Lys Leu Thr Lys Leu Phe Leu Glu Gly
20 25 30

Met His Tyr Lys Thr Leu Cys Phe Tyr Val Ile Ile Leu Asn Leu Pro
35 40 45

Phe Cys Asn Ala Ser Leu Pro Lys Gly
50 55

<210> 278
<211> 144
<212> PRT
<213> Homo sapien

<400> 278

Met Ser Ala Gly Ala Leu Phe Ile Gly Tyr Cys Ile Tyr Phe Asp Arg
1 5 10 15

Lys Arg Arg Ser Asp Pro Asn Phe Lys Asn Arg Leu Arg Glu Arg Arg

20 25 30

Lys Lys Gln Lys Leu Ala Lys Glu Arg Ala Gly Leu Ser Lys Leu Pro
35 40 45

Asp Leu Lys Asp Ala Glu Ala Val Gln Lys Phe Phe Leu Glu Glu Ile
50 55 60

Gln Leu Gly Glu Glu Leu Leu Ala Gln Glu Ala Gly His Ser Leu Gln
65 70 75 80

Leu Ala Asn Asp Asp His Val Asp Met Leu Ser Gly Leu Gln Asp Leu
85 90 95

Leu Gln Pro Val Asp Val Val Arg Val Gly Val Pro Glu Arg Asp Val
100 105 110

Arg Trp Trp Leu Thr Pro Ala Ile Pro Ala Leu Trp Glu Ala Lys Ala
115 120 125

Gly Gly Ser Leu Glu Pro Arg Arg Ser Arg Pro Val Trp Ala Thr Trp
130 135 140

<210> 279
<211> 105
<212> PRT
<213> Homo sapien

<400> 279

Phe Phe Leu Gln Asn Ala Val Gly Gln Pro Ala Arg Gly Leu Glu Thr
1 5 10 15

Arg Leu Leu Arg Ala Gln Ser Ser Gly Trp Ala Ala Ala Leu Cys Ala
20 25 30

Ala Ser Arg Ser Ser Gly Ser Gly Val Ser Ala Glu Gln Gly Glu Gly
35 40 45

Arg Arg Ser Arg Ile Leu Asn Thr Ser Ser Leu Lys Arg Gly Lys Glu
50 55 60

Gly Gly Gly Lys Asn Pro Leu Tyr Trp Lys Thr Asn Asn Pro Arg Lys
65 70 75 80

Leu Thr Trp Ser Glu Pro Ile Phe Lys Val Arg Lys Tyr Asn Gly Asp
85 90 95

Phe Ala Thr Leu Leu Tyr Gly Lys Asp
100 105

<210> 280
<211> 295
<212> PRT
<213> Homo sapien

<400> 280

Met Glu Thr Pro Ala Trp Pro Arg Val Pro Arg Pro Glu Thr Ala Val
1 5 10 15

Ala Arg Thr Leu Leu Leu Gly Trp Val Phe Ala Gln Val Ala Gly Ala
20 25 30

Ser Gly Thr Thr Asn Thr Val Ala Ala Tyr Asn Leu Thr Trp Lys Ser
35 40 45

Thr Asn Phe Lys Thr Ile Leu Glu Trp Glu Pro Lys Pro Val Asn Gln
50 55 60

Val Tyr Thr Val Gln Ile Ser Thr Lys Ser Gly Asp Trp Lys Ser Lys
65 70 75 80

Cys Phe Tyr Thr Thr Asp Thr Glu Cys Asp Leu Thr Asp Glu Ile Val
85 90 95

Lys Asp Val Lys Gln Thr Tyr Leu Ala Arg Val Phe Ser Tyr Pro Ala
100 105 110

Gly Asn Val Glu Ser Thr Gly Ser Ala Gly Glu Pro Leu Tyr Glu Asn
115 120 125

Ser Pro Glu Phe Thr Pro Tyr Leu Glu Thr Asn Leu Gly Gln Pro Thr
130 135 140

Ile Gln Ser Phe Glu Gln Val Gly Thr Lys Val Asn Val Thr Val Glu
145 150 155 160

Asp Glu Arg Thr Leu Val Arg Arg Asn Asn Thr Phe Leu Ser Leu Arg
165 170 175

Asp Val Phe Gly Lys Asp Leu Ile Tyr Thr Leu Tyr Tyr Trp Lys Ser
180 185 190

Ser Ser Ser Gly Lys Lys Thr Ala Lys Thr Asn Thr Asn Glu Phe Leu

195 200 205

Ile Asp Val Asp Lys Gly Glu Asn Tyr Cys Phe Ser Val Gln Ala Val
210 215 220

Ile Pro Ser Arg Thr Val Asn Arg Lys Ser Thr Asp Ser Pro Val Glu
225 230 235 240

Cys Met Gly Gln Glu Lys Gly Glu Phe Arg Glu Ile Phe Tyr Ile Ile
245 250 255

Gly Ala Val Val Phe Val Val Ile Ile Leu Val Ile Ile Leu Ala Ile
260 265 270

Ser Leu His Lys Cys Arg Lys Ala Gly Val Gly Gln Ser Trp Lys Glu
275 280 285

Asn Ser Pro Leu Asn Val Ser
290 295

<210> 281
<211> 67
<212> PRT
<213> Homo sapien

<400> 281

Met Glu Thr Pro Ala Trp Pro Arg Val Pro Arg Pro Glu Thr Ala Val
1 5 10 15

Ala Arg Thr Leu Leu Leu Gly Trp Val Phe Ala Gln Val Ala Gly Ala
20 25 30

Ser Gly Leu Gly Arg Gly Asn Pro Lys Gly Leu Asp Cys Cys Leu Asp
35 40 45

Trp Ser Arg Tyr Asn Val Val His Ala Pro Tyr Phe Tyr Glu Val Phe
50 55 60

Gly Thr Ala
65

<210> 282
<211> 76
<212> PRT
<213> Homo sapien

<400> 282

Met Ile Gly Leu Val Pro Ala Ser Ala Arg Val Gly Val Gln Arg Phe
1 5 10 15

Gly Tyr Tyr Leu Ser Leu Tyr Val His Leu Pro Leu Ile Lys Ser Val
20 25 30

Pro Gly Leu Phe Leu Ala Ile Phe Val Leu Gly Leu Gly Arg Gly Asn
35 40 45

Pro Lys Gly Leu Asp Cys Cys Leu Asp Trp Ser Arg Tyr Asn Val Val
50 55 60

His Ala Pro Tyr Phe Tyr Glu Val Phe Gly Thr Ala
65 70 75

<210> 283
<211> 129
<212> PRT
<213> Homo sapien

<400> 283

Met Ser Ser Pro Ile Asn Ser Asp Val Arg Leu Phe Gly Ser Arg Ser
1 5 10 15

Phe Leu Ser His Glu Thr Val Lys Lys Tyr Pro Ala Pro Leu Ala Ala
20 25 30

Val Leu Ile Lys Val Asp Pro Arg Val Leu Pro Cys Gly Ser Lys Lys
35 40 45

Arg Gln Leu Ala His Leu Leu Thr Pro Ser Arg Gln Arg Arg Gln Gln
50 55 60

Gln Ala Gly Pro Pro Pro Ser His Ala Asn His Pro Arg Glu Cys Ser
65 70 75 80

Trp Ala Pro Pro Ala Pro Pro Arg Gln Cys Ser Trp Gly Val Cys Gly
85 90 95

Glu Asp Ala Ile Gln Gly Ala Val Arg Ser Ser Ser Ser Ser Pro Ser
100 105 110

Cys Trp Thr Arg Ser Ala Trp Ser Phe Cys Cys Trp Gly Ser Trp Pro
115 120 125

Pro

<210> 284
<211> 129
<212> PRT
<213> Homo sapien

<400> 284

Met Ser Ser Pro Ile Asn Ser Asp Val Arg Leu Phe Gly Ser Arg Ser
1 5 10 15

Phe Leu Ser His Glu Thr Val Lys Lys Tyr Pro Ala Pro Leu Ala Ala
20 25 30

Val Leu Ile Lys Val Asp Pro Arg Val Leu Pro Cys Gly Ser Lys Lys
35 40 45

Arg Gln Leu Ala His Leu Leu Thr Pro Ser Arg Gln Arg Arg Gln Gln
50 55 60

Gln Ala Gly Pro Pro Pro Ser His Ala Asn His Pro Arg Glu Cys Ser
65 70 75 80

Trp Ala Pro Pro Ala Pro Pro Arg Gln Cys Ser Trp Gly Val Cys Gly
85 90 95

Glu Asp Ala Ile Gln Gly Ala Val Arg Ser Ser Ser Ser Ser Pro Ser
100 105 110

Cys Trp Thr Arg Ser Ala Trp Ser Phe Cys Cys Trp Gly Ser Trp Pro
115 120 125

Pro

<210> 285
<211> 52
<212> PRT
<213> Homo sapien

<400> 285

Met Gln Ile Met Pro His Ile Ile Leu Phe Phe Cys Cys Thr Val Ile
1 5 10 15

Cys Ser Thr Phe Glu Ile Gln Lys Tyr Ile Thr Ile Ser Gln Gly Ala
20 25 30

Ala Gly Phe Pro Gly Ala Arg Gly Leu Pro Gly Pro Pro Gly Ser Asn

35 40 45

Val Ser Asn Cys
50

<210> 286
<211> 347
<212> PRT
<213> Homo sapien

<400> 286

Met Val Asn Leu Val Val Lys Glu Lys Glu Gly Leu Arg Val Arg Lys
1 5 10 15

Val Lys Glu Ala Leu Leu Glu Leu Gln Asp Pro Leu Glu Val Leu Asp
20 25 30

Leu Leu Val Leu Leu Val Pro Lys Val Ser Lys Val Asn Val Ala Val
35 40 45

Leu Val Asp Leu Val Leu Leu Ala Ser Leu Val Leu Val Val Phe Leu
50 55 60

Val Leu Leu Val Val Met Val Thr Gln Asp Pro Gln Val Pro Ala Val
65 70 75 80

Leu Gln Ala Arg Met Gly Pro Gln Val Leu Arg Val Thr Leu Val Leu
85 90 95

Leu Ala Ala Leu Glu Cys Leu Asp Gln Lys Val Met Leu Ala Asn Gln
100 105 110

Glu Arg Arg Asp Arg Leu Val Pro Arg Ala His Gln Glu Leu Gln Ala
115 120 125

His Leu Gly Leu Leu Gly Ser Leu Glu His Gly Val Leu Gln Asp His
130 135 140

Gln Ala Cys Gln Val Leu Gly Glu Ala Leu Ala Leu Arg Val Ser Arg
145 150 155 160

Val Lys Val Gly Asn Gln Glu Leu Thr Val Ser Val Glu Asn Val Val
165 170 175

Pro Leu Asp Pro Arg Val Phe Leu Val Trp Leu Val Gln Leu Val Asn
180 185 190

Leu Glu Glu Met Glu Thr Leu Asp Gln Met Val Phe Gln Ala Glu Met
195 200 205

Asp Leu Leu Val Ala Arg Val Ile Val Val Lys Met Ala Leu Leu Val
210 215 220

Pro Leu Ala Leu Leu Val Ile Gln Ala His Leu Val Leu Ser Val Gln
225 230 235 240

Leu Glu Arg Val Val Thr Glu Glu Lys Val Ala Leu Leu Ala Leu Leu
245 250 255

Val Leu Pro Val Leu Leu Val Pro Glu Val Leu Leu Val Leu Lys Ala
260 265 270

His Val Val Thr Lys Val Lys Gln Val Asn Val Glu Leu Leu Ala Ser
275 280 285

Lys Asp Ile Glu Asp Ser Leu Val Ile Gln Val Pro Gln Val Leu Gln
290 295 300

Ala Leu Leu Val Ser Arg Val Gln Ser Ala Val Gln Asp Leu Gln Ala
305 310 315 320

Pro Glu Asp Pro Val Gly Pro Met Trp Thr Pro Gly Lys Asp Gly Pro
325 330 335

Val Gly Ser Arg Pro Trp Thr Thr Gly Leu Glu
340 345

<210> 287
<211> 327
<212> PRT
<213> Homo sapien

<400> 287

Met Gln Ile Met Pro His Ile Ile Leu Phe Val Cys Cys Thr Val Ile
1 5 10 15

Cys Ser Thr Phe Glu Ile Gln Lys Tyr Ile Thr Ile Ser Gln Gly Pro
20 25 30

Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu Pro Gly Pro Pro Gly
35 40 45

Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser Gly Ser Pro Gly Lys

50 55 60

Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly Ala Pro Gly Ser Pro
65 70 75 80

Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln Pro Gly Glu Lys Gly
85 90 95

Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro Gly Pro Leu Gly Ile
100 105 110

Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro
115 120 125

Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val Lys Gly Glu Ser Gly
130 135 140

Lys Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg Gly Pro Pro Gly Pro
145 150 155 160

Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly Glu Pro Gly Arg Asp
165 170 175

Gly Asn Pro Gly Ser Asp Gly Leu Pro Gly Arg Asp Gly Ser Pro Gly
180 185 190

Gly Lys Gly Asp Arg Gly Glu Asn Gly Ser Pro Gly Ala Pro Gly Ala
195 200 205

Pro Gly His Pro Gly Pro Pro Gly Pro Val Gly Pro Ala Gly Lys Ser
210 215 220

Gly Asp Arg Gly Glu Ser Gly Pro Ala Gly Pro Ala Gly Ala Pro Gly
225 230 235 240

Pro Ala Gly Ser Arg Gly Ala Pro Gly Pro Gln Gly Pro Arg Gly Asp
245 250 255

Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly Ile Lys Gly His Arg
260 265 270

Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser Pro Gly Pro Ala Gly
275 280 285

Gln Gln Gly Ala Ile Gly Ser Pro Gly Pro Ala Gly Pro Arg Gly Pro
290 295 300

Val Gly Pro Met Trp Thr Pro Gly Lys Asp Gly Pro Val Gly Ser Arg
305 310 315 320

Pro Trp Thr Thr Gly Leu Glu
325

<210> 288
<211> 702
<212> PRT
<213> Homo sapien

<400> 288

Gln Gly Pro Pro Gly Glu Pro Gly Gln Ala Gly Pro Ser Gly Pro Pro
1 5 10 15

Gly Pro Pro Gly Ala Ile Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly
20 25 30

Glu Ser Gly Arg Pro Gly Arg Pro Gly Glu Arg Gly Leu Pro Gly Pro
35 40 45

Pro Gly Ile Lys Gly Pro Ala Gly Ile Pro Gly Phe Pro Gly Met Lys
50 55 60

Gly His Arg Gly Phe Asp Gly Arg Asn Gly Glu Lys Gly Glu Thr Gly
65 70 75 80

Ala Pro Gly Leu Lys Gly Glu Asn Gly Leu Pro Gly Glu Asn Gly Ala
85 90 95

Pro Gly Pro Met Gly Pro Arg Gly Ala Pro Gly Glu Arg Gly Arg Pro
100 105 110

Gly Leu Pro Gly Ala Ala Gly Ala Arg Gly Asn Asp Gly Ala Arg Gly
115 120 125

Ser Asp Gly Gln Pro Gly Pro Pro Gly Pro Pro Gly Thr Ala Gly Phe
130 135 140

Pro Gly Ser Pro Gly Ala Lys Gly Glu Val Gly Pro Ala Gly Ser Pro
145 150 155 160

Gly Ser Asn Gly Ala Pro Gly Gln Arg Gly Glu Pro Gly Pro Gln Gly
165 170 175

His Ala Gly Ala Gln Gly Pro Pro Gly Pro Pro Gly Ile Asn Gly Ser
180 185 190

Pro Gly Gly Lys Gly Glu Met Gly Pro Ala Gly Ile Pro Gly Ala Pro
195 200 205

Gly Leu Met Gly Ala Arg Gly Pro Pro Gly Pro Ala Gly Ala Asn Gly
210 215 220

Ala Pro Gly Leu Arg Gly Gly Ala Gly Glu Pro Gly Lys Asn Gly Ala
225 230 235 240

Lys Gly Glu Pro Gly Pro Arg Gly Glu Arg Gly Glu Ala Gly Ile Pro
245 250 255

Gly Val Pro Gly Ala Lys Gly Glu Asp Gly Lys Asp Gly Ser Pro Gly
260 265 270

Glu Pro Gly Ala Asn Gly Leu Pro Gly Ala Ala Gly Glu Arg Gly Ala
275 280 285

Pro Gly Phe Arg Gly Pro Ala Gly Pro Asn Gly Ile Pro Gly Glu Lys
290 295 300

Gly Pro Ala Gly Glu Arg Gly Ala Pro Gly Pro Ala Gly Pro Arg Gly
305 310 315 320

Ala Ala Gly Glu Pro Gly Arg Asp Gly Val Pro Gly Gly Pro Gly Met
325 330 335

Arg Gly Met Pro Gly Ser Pro Gly Gly Pro Gly Ser Asp Gly Lys Pro
340 345 350

Gly Pro Pro Gly Ser Gln Gly Glu Ser Gly Arg Pro Gly Pro Pro Gly
355 360 365

Pro Ser Gly Pro Arg Gly Gln Pro Gly Val Met Gly Phe Pro Gly Pro
370 375 380

Lys Gly Asn Asp Gly Ala Pro Gly Lys Asn Gly Glu Arg Gly Gly Pro
385 390 395 400

Gly Gly Pro Gly Pro Gln Gly Pro Pro Gly Lys Asn Gly Glu Thr Gly
405 410 415

Pro Gln Gly Pro Pro Gly Pro Thr Gly Pro Gly Gly Asp Lys Gly Asp

420 425 430

Thr Gly Pro Pro Gly Pro Gln Gly Leu Gln Gly Leu Pro Gly Thr Gly
435 440 445

Gly Pro Pro Gly Glu Asn Gly Lys Pro Gly Glu Pro Gly Pro Lys Gly
450 455 460

Asp Ala Gly Ala Pro Gly Ala Pro Gly Gly Lys Gly Asp Ala Gly Ala
465 470 475 480

Pro Gly Glu Arg Gly Pro Pro Gly Leu Ala Gly Ala Pro Gly Leu Arg
485 490 495

Gly Gly Ala Gly Pro Pro Gly Pro Glu Gly Gly Lys Gly Ala Ala Gly
500 505 510

Pro Pro Gly Pro Pro Gly Ala Ala Gly Thr Pro Gly Leu Gln Gly Met
515 520 525

Pro Gly Glu Arg Gly Gly Leu Gly Ser Pro Trp Ser Ser Gln Arg Trp
530 535 540

Phe Arg Leu Gln Leu Pro Ala Pro Ala Thr Ser Arg Glu Gly Ser Arg
545 550 555 560

Gly Gly Arg Tyr Tyr Arg Ala Asp Asp Ala Asn Val Val Arg Asp Arg
565 570 575

Asp Leu Glu Val Asp Thr Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu
580 585 590

Asn Ile Arg Ser Pro Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys
595 600 605

Arg Asp Leu Lys Met Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp
610 615 620

Ile Asp Pro Asn Gln Gly Cys Asn Leu Asp Ala Ile Lys Val Phe Cys
625 630 635 640

Asn Met Glu Thr Gly Glu Thr Cys Val Tyr Pro Thr Gln Pro Ser Val
645 650 655

Ala Gln Lys Asn Trp Tyr Ile Asn Lys Asn Pro Lys Asp Lys Arg His
660 665 670

Val Trp Phe Gly Glu Ser Met Thr Asp Gly Ile Pro Phe Gln Phe Gly
675 680 685

Gly Gln Gly Phe Asp Pro Ser Asp Val Ala Ile Gln Leu Thr
690 695 700

<210> 289
<211> 82
<212> PRT
<213> Homo sapien

<400> 289

Gln Val Pro His Ala Ser Gly Cys Ile Gly Glu Asp Pro Gln Gly Ile
1 5 10 15

Pro Leu Pro Leu Asp Glu Ala His Pro Thr Gly Gly Cys Thr Asn Pro
20 25 30

Tyr Gly Lys Ser Lys Phe Phe Ile Glu Glu Met Ile Arg Asp Leu Cys
35 40 45

Gln Ala Asp Lys Gly Trp Thr Ala Ala Leu Gly Leu Asp Arg Met Cys
50 55 60

Glu Asp Leu Trp Arg Trp Gln Lys Gln Asn Pro Ser Gly Phe Gly Thr
65 70 75 80

Gln Ala

<210> 290
<211> 360
<212> PRT
<213> Homo sapien

<400> 290

Met Ala Glu Lys Val Leu Val Thr Gly Gly Ala Gly Tyr Ile Gly Ser
1 5 10 15

His Thr Val Leu Glu Leu Leu Glu Ala Gly Tyr Leu Pro Val Val Ile
20 25 30

Asp Asn Phe His Asn Ala Phe Arg Gly Gly Gly Ser Leu Pro Glu Ser
35 40 45

Leu Arg Arg Val Gln Glu Leu Thr Gly Arg Ser Val Glu Phe Glu Glu

50 55 60

Met Asp Ile Leu Asp Gln Gly Ala Leu Gln Arg Leu Phe Lys Lys Tyr
65 70 75 80

Ser Phe Met Ala Val Ile His Phe Ala Gly Leu Lys Ala Val Gly Glu
85 90 95

Ser Val Gln Lys Pro Leu Asp Tyr Tyr Arg Val Asn Leu Thr Gly Thr
100 105 110

Ile Gln Leu Leu Glu Ile Met Lys Ala His Gly Val Lys Asn Leu Val
115 120 125

Phe Ser Ser Ser Ala Thr Val Tyr Gly Asn Pro Gln Tyr Leu Pro Leu
130 135 140

Asp Glu Ala His Pro Thr Gly Gly Cys Thr Asn Pro Tyr Gly Lys Ser
145 150 155 160

Lys Phe Phe Ile Glu Glu Met Ile Arg Asp Leu Cys Gln Ala Asp Lys
165 170 175

Thr Trp Asn Ala Val Leu Leu Arg Tyr Phe Asn Pro Thr Gly Ala His
180 185 190

Ala Ser Gly Cys Ile Gly Glu Asp Pro Gln Gly Ile Pro Asn Asn Leu
195 200 205

Met Pro Tyr Val Ser Gln Val Ala Ile Gly Arg Arg Glu Ala Leu Asn
210 215 220

Val Phe Gly Asn Asp Tyr Asp Thr Glu Asp Gly Thr Gly Val Arg Asp
225 230 235 240

Tyr Ile His Val Val Asp Leu Ala Lys Gly His Ile Ala Ala Leu Arg
245 250 255

Lys Leu Lys Glu Gln Cys Gly Cys Arg Val Gly Arg Glu Gly Arg Ser
260 265 270

Glu Gly Gly Glu Gly Pro Asp Pro Gly Arg Ala Ala Gln Arg Arg Gly
275 280 285

Gln Ser Ser Pro Leu His Lys Pro Cys Ser Pro Trp Ala Arg Ser Thr
290 295 300

Thr Trp Ala Arg Ala Gln Ala Ile Gln Cys Cys Arg Trp Ser Arg Leu
305 310 315 320

Trp Arg Arg Pro Leu Gly Arg Arg Ser Arg Thr Arg Trp Trp His Gly
325 330 335

Gly Lys Val Met Trp Gln Pro Val Thr Pro Thr Pro Ala Trp Pro Lys
340 345 350

Arg Ser Trp Gly Gly Gln Gln Pro
355 360

<210> 291
<211> 466
<212> PRT
<213> Homo sapien

<400> 291

Met Ala Glu Lys Val Leu Val Thr Gly Gly Ala Gly Tyr Ile Gly Ser
1 5 10 15

His Thr Val Leu Glu Leu Leu Glu Ala Gly Tyr Leu Pro Val Val Ile
20 25 30

Asp Asn Phe His Asn Ala Phe Arg Gly Gly Gly Ser Leu Pro Glu Ser
35 40 45

Leu Arg Arg Val Gln Glu Leu Thr Gly Arg Ser Val Glu Phe Glu Glu
50 55 60

Met Asp Ile Leu Asp Gln Gly Ala Leu Gln Arg Leu Phe Lys Lys Tyr
65 70 75 80

Ser Phe Met Ala Val Ile His Phe Ala Gly Leu Lys Ala Val Gly Glu
85 90 95

Ser Val Gln Lys Pro Leu Asp Tyr Tyr Arg Val Asn Leu Thr Gly Thr
100 105 110

Ile Gln Leu Leu Glu Ile Met Lys Ala His Gly Val Lys Asn Leu Val
115 120 125

Phe Ser Ser Ser Ala Thr Val Tyr Gly Asn Pro Gln Tyr Leu Pro Leu
130 135 140

Asp Glu Ala His Pro Thr Gly Gly Cys Thr Asn Pro Tyr Gly Lys Ser
145 150 155 160

Lys Phe Phe Ile Glu Glu Met Ile Arg Asp Leu Cys Gln Ala Asp Lys
165 170 175

Thr Trp Asn Ala Val Leu Leu Arg Tyr Phe Asn Pro Thr Gly Ala His
180 185 190

Ala Ser Gly Cys Ile Gly Glu Asp Pro Gln Gly Ile Pro Asn Asn Leu
195 200 205

Met Pro Tyr Val Ser Gln Val Ala Ile Gly Arg Arg Glu Ala Leu Asn
210 215 220

Val Phe Gly Asn Asp Tyr Asp Thr Glu Asp Gly Thr Gly Val Arg Asp
225 230 235 240

Tyr Ile His Val Val Asp Leu Ala Lys Gly His Ile Ala Ala Leu Arg
245 250 255

Lys Leu Lys Glu Gln Cys Gly Cys Arg Val Gly Arg Glu Gly Arg Ser
260 265 270

Glu Gly Gly Glu Gly Pro Asp Pro Gly Arg Ala Ala Gln Arg Arg Gly
275 280 285

Gln Ser Ser Pro Leu His Lys Pro Cys Ser Pro Trp Ala Arg Ser Thr
290 295 300

Thr Trp Ala Arg Ala Gln Ala Ile Gln Cys Cys Arg Trp Ser Arg Leu
305 310 315 320

Trp Arg Arg Pro Leu Gly Arg Arg Ser Gly Pro Pro Thr Pro Pro Thr
325 330 335

Ser Pro Thr Ser Pro His Pro Ala Leu Ser Asn Arg Ala Ala Leu Ala
340 345 350

Leu Pro Thr His Leu Ser Gly Gly Tyr Leu Ala Leu Pro Ser Leu Leu
355 360 365

Ser Leu Pro Ser Thr Arg Cys Leu Arg Ala Ser Arg Cys Ser Ala Leu
370 375 380

Leu Leu Leu Lys Asp Leu Ala Ser Ser Trp Ala Arg Ala Gly Ser Ala

385 390 395 400

Lys Leu Gln Leu Pro Pro Val Leu Gln Ile Pro Tyr Lys Val Val Ala
405 410 415

Arg Arg Glu Gly Asp Val Ala Ala Cys Tyr Ala Asn Pro Ser Leu Ala
420 425 430

Gln Glu Glu Leu Gly Trp Thr Ala Ala Leu Gly Leu Asp Arg Met Cys
435 440 445

Glu Asp Leu Trp Arg Trp Gln Lys Gln Asn Pro Ser Gly Phe Gly Thr
450 455 460

Gln Ala
465

<210> 292
<211> 328
<212> PRT
<213> Homo sapien

<400> 292

Met Ala Glu Lys Val Leu Val Thr Gly Gly Ala Gly Tyr Ile Gly Ser
1 5 10 15

His Thr Val Leu Glu Leu Leu Glu Ala Gly Tyr Leu Pro Val Val Ile
20 25 30

Asp Asn Phe His Asn Ala Phe Arg Gly Gly Gly Ser Leu Pro Glu Ser
35 40 45

Leu Arg Arg Val Gln Glu Leu Thr Gly Arg Ser Val Glu Phe Glu Glu
50 55 60

Met Asp Ile Leu Asp Gln Gly Ala Leu Gln Arg Leu Phe Lys Lys Tyr
65 70 75 80

Ser Phe Met Ala Val Ile His Phe Ala Gly Leu Lys Ala Val Gly Glu
85 90 95

Ser Val Gln Lys Pro Leu Asp Tyr Tyr Arg Val Asn Leu Thr Gly Thr
100 105 110

Ile Gln Leu Leu Glu Ile Met Lys Ala His Gly Val Lys Asn Leu Val
115 120 125

Phe Ser Ser Ser Ala Thr Val Tyr Gly Asn Pro Gln Tyr Leu Pro Leu
130 135 140

Asp Glu Ala His Pro Thr Gly Gly Cys Thr Asn Pro Tyr Gly Lys Ser
145 150 155 160

Lys Phe Phe Ile Glu Glu Met Ile Arg Asp Leu Cys Gln Ala Asp Lys
165 170 175

Thr Trp Asn Ala Val Leu Leu Arg Tyr Phe Asn Pro Thr Gly Ala His
180 185 190

Ala Ser Gly Cys Ile Gly Glu Asp Pro Gln Gly Ile Pro Asn Asn Leu
195 200 205

Met Pro Tyr Val Ser Gln Val Ala Ile Gly Arg Arg Glu Ala Leu Asn
210 215 220

Val Phe Gly Asn Asp Tyr Asp Thr Glu Asp Gly Thr Gly Val Arg Asp
225 230 235 240

Tyr Ile His Val Val Asp Leu Ala Lys Gly His Ile Ala Ala Leu Arg
245 250 255

Lys Leu Lys Glu Gln Cys Gly Cys Arg Val Gly Arg Glu Gly Arg Ser
260 265 270

Glu Gly Gly Glu Gly Pro Asp Pro Gly Arg Ala Ala Gln Arg Arg Gly
275 280 285

Gln Ser Ser Pro Leu His Lys Pro Cys Ser Pro Trp Ala Arg Ser Thr
290 295 300

Thr Trp Ala Arg Ala Gln Ala Ile Gln Cys Cys Arg Trp Ser Arg Leu
305 310 315 320

Trp Arg Arg Pro Leu Gly Arg Arg
325

<210> 293
<211> 77
<212> PRT
<213> Homo sapien

<400> 293

Met Pro Ser Leu His Gly Gln Ile Met Lys Ala His Gly Val Lys Asn

1 5 10 15

Leu Val Phe Ser Ser Ser Ala Thr Val Tyr Gly Asn Pro Gln Tyr Leu
20 25 30

Pro Leu Asp Glu Ala His Pro Thr Gly Gly Cys Thr Asn Pro Tyr Gly
35 40 45

Lys Ser Lys Phe Phe Ile Glu Glu Met Ile Arg Asp Leu Cys Gln Ala
50 55 60

Asp Lys Val Arg Ala Pro Leu Thr Val Pro Trp Leu His
65 70 75

<210> 294
<211> 280
<212> PRT
<213> Homo sapien

<400> 294

Met Asp Leu Gln Gly Arg Gly Val Pro Ser Ile Asp Arg Leu Arg Val
1 5 10 15

Leu Leu Met Leu Phe His Thr Met Ala Gln Ile Met Ala Glu Gln Glu
20 25 30

Val Glu Asn Leu Ser Gly Leu Ser Thr Asn Pro Glu Lys Asp Ile Phe
35 40 45

Val Val Arg Glu Asn Gly Thr Thr Cys Leu Met Ala Glu Phe Ala Ala
50 55 60

Lys Phe Ile Val Pro Tyr Asp Val Trp Ala Ser Asn Tyr Val Asp Leu
65 70 75 80

Ile Thr Glu Gln Ala Asp Ile Ala Leu Thr Arg Gly Ala Glu Val Lys
85 90 95

Gly Arg Cys Gly His Ser Gln Ser Glu Leu Gln Val Phe Trp Val Asp
100 105 110

Arg Ala Tyr Ala Leu Lys Met Leu Phe Val Lys Glu Ser His Asn Met
115 120 125

Ser Lys Gly Pro Glu Ala Thr Trp Arg Leu Ser Lys Val Gln Phe Val
130 135 140

Tyr Asp Ser Ser Glu Lys Thr His Phe Lys Asp Ala Val Ser Ala Gly
145 150 155 160

Lys His Thr Ala Asn Ser His His Leu Ser Ala Leu Val Thr Pro Ala
165 170 175

Gly Lys Ser Tyr Glu Cys Gln Ala Gln Gln Thr Ile Ser Leu Ala Ser
180 185 190

Ser Asp Pro Gln Lys Thr Val Thr Met Ile Leu Ser Ala Val His Ile
195 200 205

Gln Pro Phe Asp Ile Ile Ser Asp Phe Val Phe Ser Glu Glu His Lys
210 215 220

Cys Pro Val Asp Glu Arg Glu Gln Leu Glu Glu Thr Leu Pro Leu Ile
225 230 235 240

Leu Gly Leu Ile Leu Gly Leu Val Ile Met Val Thr Leu Ala Ile Tyr
245 250 255

His Val His His Lys Met Thr Ala Asn Gln Val Gln Ile Pro Arg Asp
260 265 270

Arg Ser Gln Tyr Lys His Met Gly
275 280

<210> 295
<211> 173
<212> PRT
<213> Homo sapien

<400> 295

Met Asp Leu Gln Gly Arg Gly Val Pro Ser Ile Asp Arg Leu Arg Val
1 5 10 15

Leu Leu Met Leu Phe His Thr Met Ala Gln Ile Met Ala Glu Gln Glu
20 25 30

Val Glu Asn Leu Ser Gly Leu Ser Thr Asn Pro Glu Lys Asp Ile Phe
35 40 45

Val Val Arg Glu Asn Gly Thr Thr Cys Leu Met Ala Glu Phe Ala Ala
50 55 60

Lys Phe Ile Val Pro Tyr Asp Val Trp Ala Ser Asn Tyr Val Asp Leu

65 70 75 80

Ile Thr Glu Gln Ala Asp Ile Ala Leu Thr Arg Gly Ala Glu Val Lys
85 90 95

Gly Arg Cys Gly His Ser Gln Ser Glu Leu Gln Val Phe Trp Val Asp
100 105 110

Arg Ala Tyr Ala Leu Lys Met Leu Phe Val Lys Val Thr Pro Ser Pro
115 120 125

Ala Gly Arg Gly Ala Ala Gly Ser Ala Trp Val Trp Glu Val Ala Ala
130 135 140

Pro Arg Phe Lys Asn Pro Asp Ala Ala Gly Thr Ile Glu Ala His Leu
145 150 155 160

Pro Gly Ser Thr Gly Lys Pro Gln His Val Gln Gly Thr
165 170

<210> 296
<211> 90
<212> PRT
<213> Homo sapien

<400> 296

Met Asp Leu Gln Gly Arg Gly Val Pro Ser Ile Asp Arg Leu Arg Val
1 5 10 15

Leu Leu Met Leu Phe His Thr Met Ala Gln Ile Met Ala Glu Gln Glu
20 25 30

Val Glu Asn Leu Ser Gly Leu Ser Thr Asn Pro Glu Lys Asp Ile Phe
35 40 45

Val Val Arg Glu Asn Gly Thr Thr Leu Trp Pro Gln Pro Val Gly Ala
50 55 60

Ala Ser Val Leu Gly Gly Ser Arg Ile Cys Thr Gln Asn Ala Leu Cys
65 70 75 80

Lys Gly Lys Pro Gln His Val Gln Gly Thr
85 90

<210> 297
<211> 280
<212> PRT

<213> Homo sapien

<400> 297

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Met Asp Leu Gln Gly Arg Gly Val Pro Ser Ile Asp Arg Leu Arg Val
1               5                  10                  15

Leu Leu Met Leu Phe His Thr Met Ala Gln Ile Met Ala Glu Gln Glu
            20                  25                  30

Val Glu Asn Leu Ser Gly Leu Ser Thr Asn Pro Glu Lys Asp Ile Phe
        35                  40                  45

Val Val Arg Glu Asn Gly Thr Thr Cys Leu Met Ala Glu Phe Ala Ala
    50                  55                  60

Lys Phe Ile Val Pro Tyr Asp Val Trp Ala Ser Asn Tyr Val Asp Leu
65                  70                  75                  80

Ile Thr Glu Gln Ala Asp Ile Ala Leu Thr Arg Gly Ala Glu Val Lys
                85                  90                  95

Gly Arg Cys Gly His Ser Gln Ser Glu Leu Gln Val Phe Trp Val Asp
            100                 105                 110

Arg Ala Tyr Ala Leu Lys Met Leu Phe Val Lys Glu Ser His Asn Met
        115                 120                 125

Ser Lys Gly Pro Glu Ala Thr Trp Arg Leu Ser Lys Val Gln Phe Val
    130                 135                 140

Tyr Asp Ser Ser Glu Lys Thr His Phe Lys Asp Ala Val Ser Ala Gly
145                 150                 155                 160

Lys His Thr Ala Asn Ser His His Leu Ser Ala Leu Val Thr Pro Ala
                165                 170                 175

Gly Lys Ser Tyr Glu Cys Gln Ala Gln Gln Thr Ile Ser Leu Ala Ser
            180                 185                 190

Ser Asp Pro Gln Lys Thr Val Thr Met Ile Leu Ser Ala Val His Ile
        195                 200                 205

Gln Pro Phe Asp Ile Ile Ser Asp Phe Val Phe Ser Glu Glu His Lys
    210                 215                 220

Cys Pro Val Asp Glu Arg Glu Gln Leu Glu Glu Thr Leu Pro Leu Ile
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225 230 235 240

Leu Gly Leu Ile Leu Gly Leu Val Ile Met Val Thr Leu Ala Ile Tyr
245 250 255

His Val His His Lys Met Thr Ala Asn Gln Val Gln Ile Pro Arg Asp
260 265 270

Arg Ser Gln Tyr Lys His Met Gly
275 280

<210> 298
<211> 321
<212> PRT
<213> Homo sapien

<400> 298

Met Asp Leu Gln Gly Arg Gly Val Pro Ser Ile Asp Arg Leu Arg Val
1 5 10 15

Leu Leu Met Leu Phe His Thr Met Ala Gln Ile Met Ala Glu Gln Glu
20 25 30

Val Glu Asn Leu Ser Gly Leu Ser Thr Asn Pro Glu Lys Asp Ile Phe
35 40 45

Val Val Arg Glu Asn Gly Thr Thr Cys Leu Met Ala Glu Phe Ala Ala
50 55 60

Lys Phe Ile Val Pro Tyr Asp Val Trp Ala Ser Asn Tyr Val Asp Leu
65 70 75 80

Ile Thr Glu Gln Ala Asp Ile Ala Leu Thr Arg Gly Ala Glu Val Lys
85 90 95

Gly Arg Cys Gly His Ser Gln Ser Glu Leu Gln Val Phe Trp Val Asp
100 105 110

Arg Ala Tyr Ala Leu Lys Met Leu Phe Val Lys Val Thr Pro Ser Pro
115 120 125

Ala Gly Arg Gly Ala Ala Gly Ser Ala Trp Val Trp Glu Val Ala Ala
130 135 140

Pro Arg Phe Lys Asn Pro Glu Leu Arg Gly Arg Leu Lys Arg Thr Ser
145 150 155 160

Pro Ala Gln Gln Glu Ser His Asn Met Ser Lys Gly Pro Glu Ala Thr
165 170 175

Trp Arg Leu Ser Lys Val Gln Phe Val Tyr Asp Ser Ser Glu Lys Thr
180 185 190

His Phe Lys Asp Ala Val Ser Ala Gly Lys His Thr Ala Asn Ser His
195 200 205

His Leu Ser Ala Leu Val Thr Pro Ala Gly Lys Ser Tyr Glu Cys Gln
210 215 220

Ala Gln Gln Thr Ile Ser Leu Ala Ser Ser Asp Pro Gln Lys Thr Val
225 230 235 240

Thr Met Ile Leu Ser Ala Val His Ile Gln Pro Phe Asp Ile Ile Ser
245 250 255

Asp Phe Val Phe Ser Glu Glu His Lys Cys Pro Val Asp Glu Arg Glu
260 265 270

Gln Leu Glu Glu Thr Leu Pro Leu Ile Leu Gly Leu Ile Leu Gly Leu
275 280 285

Val Ile Met Val Thr Leu Ala Ile Tyr His Val His His Lys Met Thr
290 295 300

Ala Asn Gln Val Gln Ile Pro Arg Asp Arg Ser Gln Tyr Lys His Met
305 310 315 320

Gly

<210> 299
<211> 373
<212> PRT
<213> Homo sapien

<400> 299

Arg Thr Val Thr Val Arg Thr Arg Ile Ala Val Leu Ser Leu Arg Pro
1 5 10 15

Gln Cys Gly Gly Ile Leu Phe Arg His Val Val Val Leu Thr Leu Gly
20 25 30

Asn Gly Leu Gly Gln Asn Leu Asp Leu Ala Ser Val Gln Ala His Ala

35 40 45

Ala Val Gln Gly Arg Arg Val Leu Ile Pro Gly Val Asn Ile Arg Gln
50 55 60

Glu Asn Leu Gly Arg Gly Arg Phe His Asp His Val Gln Asp Ala Ala
65 70 75 80

Val Gly Gly Val Gly Gln Ala Leu Arg Cys His Gln His Lys Ala Val
85 90 95

Gly Leu Thr Gln His Leu Glu Pro Phe Pro Asp Leu Arg Ala Glu Cys
100 105 110

Arg Val Ala Glu His Gln Pro Gly Phe Val Gln Asp Asp Glu Arg Pro
115 120 125

Pro Val Trp Trp Asn Ser Asn Pro Glu Lys Asp Ile Phe Val Val Arg
130 135 140

Glu Asn Gly Thr Thr Cys Leu Met Ala Glu Phe Ala Ala Lys Phe Ile
145 150 155 160

Val Pro Tyr Asp Val Trp Ala Ser Asn Tyr Val Asp Leu Ile Thr Glu
165 170 175

Gln Ala Asp Ile Ala Leu Thr Arg Gly Ala Glu Val Lys Gly Arg Cys
180 185 190

Gly His Ser Gln Ser Glu Leu Gln Val Phe Trp Val Asp Arg Ala Tyr
195 200 205

Ala Leu Lys Met Leu Phe Val Lys Glu Ser His Asn Met Ser Lys Gly
210 215 220

Pro Glu Ala Thr Trp Arg Leu Ser Lys Val Gln Phe Val Tyr Asp Ser
225 230 235 240

Ser Glu Lys Thr His Phe Lys Asp Ala Val Ser Ala Gly Lys His Thr
245 250 255

Ala Asn Ser His His Leu Ser Ala Leu Val Thr Pro Ala Gly Lys Ser
260 265 270

Tyr Glu Cys Gln Ala Gln Gln Thr Ile Ser Leu Ala Ser Ser Asp Pro
275 280 285

Gln Lys Thr Val Thr Met Ile Leu Ser Ala Val His Ile Gln Pro Phe
290 295 300

Asp Ile Ile Ser Asp Phe Val Phe Ser Glu Glu His Lys Cys Pro Val
305 310 315 320

Asp Glu Arg Glu Gln Leu Glu Glu Thr Leu Pro Leu Ile Leu Gly Leu
325 330 335

Ile Leu Gly Leu Val Ile Met Val Thr Leu Ala Ile Tyr His Val His
340 345 350

His Lys Met Thr Ala Asn Gln Val Gln Ile Pro Arg Asp Arg Ser Gln
355 360 365

Tyr Lys His Met Gly
370

<210> 300
<211> 363
<212> PRT
<213> Homo sapien

<400> 300

Met Lys Thr Leu Leu Leu Leu Leu Leu Val Leu Leu Glu Leu Gly Glu
1 5 10 15

Ala Gln Gly Ser Leu His Arg Val Pro Leu Arg Arg His Pro Ser Leu
20 25 30

Lys Lys Lys Leu Arg Ala Arg Ser Gln Leu Ser Glu Phe Trp Lys Ser
35 40 45

His Asn Leu Asp Met Ile Gln Phe Thr Glu Ser Cys Ser Met Asp Gln
50 55 60

Ser Ala Lys Glu Pro Leu Ile Asn Tyr Leu Asp Met Glu Tyr Phe Gly
65 70 75 80

Thr Ile Ser Ile Gly Ser Pro Pro Gln Asn Phe Thr Val Ile Phe Asp
85 90 95

Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Val Tyr Cys Thr Ser Pro
100 105 110

Ala Cys Lys Thr His Ser Arg Phe Gln Pro Ser Gln Ser Ser Thr Tyr
115 120 125

Ser Gln Pro Gly Gln Ser Phe Ser Ile Gln Tyr Gly Thr Gly Ser Leu
130 135 140

Ser Gly Ile Ile Gly Ala Asp Gln Val Ser Val Glu Gly Leu Thr Val
145 150 155 160

Val Gly Gln Gln Phe Gly Glu Ser Val Thr Glu Pro Gly Gln Thr Phe
165 170 175

Val Asp Ala Glu Phe Asp Gly Ile Leu Gly Leu Gly Tyr Pro Ser Leu
180 185 190

Ala Val Gly Gly Val Thr Pro Val Phe Asp Asn Met Met Ala Gln Asn
195 200 205

Leu Val Asp Leu Pro Met Phe Ser Val Tyr Met Ser Ser Asn Pro Glu
210 215 220

Gly Gly Ala Gly Ser Glu Leu Ile Phe Gly Gly Tyr Asp His Ser His
225 230 235 240

Phe Ser Gly Ser Leu Asn Trp Val Pro Val Thr Lys Gln Ala Tyr Trp
245 250 255

Gln Ile Ala Leu Asp Asn Met Leu Trp Ser Val Pro Thr Leu Thr Ser
260 265 270

Cys Arg Met Ser Pro Ser Pro Leu Thr Glu Ser Pro Ile Pro Ser Ala
275 280 285

Gln Leu Pro Thr Pro Tyr Trp Thr Ser Trp Met Glu Cys Ser Ser Ala
290 295 300

Ala Val Ala Phe Lys Asp Leu Thr Ser Thr Leu Gln Leu Gly Pro Ser
305 310 315 320

Gly Ser Trp Gly Met Ser Ser Phe Asp Ser Phe Thr Gln Ser Leu Thr
325 330 335

Val Gly Ile Thr Val Trp Asp Trp Pro Gln Gln Ser Pro Lys Glu Gly
340 345 350

Pro Cys Val Cys Ala Cys Leu Ser Asp Arg Pro

355 360

<210> 301
<211> 282
<212> PRT
<213> Homo sapien

<400> 301

Met Gly Cys Trp Gly Arg Asn Arg Gly Arg Leu Leu Cys Met Leu Ala
1 5 10 15

Leu Thr Phe Met Phe Met Val Leu Glu Val Val Val Ser Arg Val Thr
20 25 30

Ser Ser Leu Ala Met Leu Ser Asp Ser Phe His Met Leu Ser Asp Val
35 40 45

Leu Ala Leu Val Val Ala Leu Val Ala Glu Arg Phe Ala Arg Arg Thr
50 55 60

His Ala Thr Gln Lys Asn Thr Phe Gly Trp Ile Arg Ala Glu Val Met
65 70 75 80

Gly Ala Leu Val Asn Ala Ile Phe Leu Thr Gly Leu Cys Phe Ala Ile
85 90 95

Leu Leu Glu Ala Ile Glu Arg Phe Ile Glu Pro His Glu Met Gln Gln
100 105 110

Pro Leu Val Val Leu Gly Val Gly Val Ala Gly Leu Leu Val Asn Val
115 120 125

Leu Gly Leu Cys Leu Phe His His His Ser Gly Phe Ser Gln Asp Ser
130 135 140

Gly His Gly His Ser His Gly Gly His Gly His Gly His Gly Leu Pro
145 150 155 160

Lys Gly Pro Arg Val Lys Ser Thr Arg Pro Gly Ser Ser Asp Ile Asn
165 170 175

Val Ala Pro Gly Glu Gln Gly Pro Asp Gln Glu Glu Thr Asn Thr Leu
180 185 190

Val Ala Asn Thr Ser Asn Ser Asn Gly Leu Lys Leu Asp Pro Ala Gly
195 200 205

Glu Pro Gly Lys Ser Leu Pro Gln Val Val Gly Phe Gly Val Pro Arg
210 215 220

Ala Ser Pro Gly Leu Arg Arg Gly Gly Pro His Ala Pro Cys Cys Pro
225 230 235 240

Ser Gly Pro Ala Pro Arg Arg Pro Cys Leu Leu Pro Pro Arg Pro Ala
245 250 255

His Ala Pro Leu Leu Leu Gln Glu Ile Arg Thr Pro Ser Val Gly Cys
260 265 270

Lys Glu Pro Ala Thr Arg Leu Ala Tyr Leu
275 280

<210> 302
<211> 177
<212> PRT
<213> Homo sapien

<400> 302

Ala Thr Ala Leu Lys Asp Val Val Lys Val Gly Ala Val Asp Ala Asp
1 5 10 15

Lys His His Ser Leu Gly Gly Gln Tyr Gly Val Gln Gly Phe Pro Thr
20 25 30

Ile Lys Ile Phe Gly Ser Asn Lys Asn Arg Pro Glu Asp Tyr Gln Gly
35 40 45

Gly Arg Thr Gly Glu Ala Ile Val Asp Ala Ala Leu Ser Ala Leu Arg
50 55 60

Gln Leu Val Lys Asp Arg Leu Gly Gly Arg Ser Lys Asp Val Leu Asp
65 70 75 80

Ser Glu Asp Val Trp Met Val Glu Phe Tyr Ala Pro Trp Cys Gly His
85 90 95

Cys Lys Asn Leu Glu Pro Glu Trp Ala Ala Ala Ala Ser Glu Val Lys
100 105 110

Glu Gln Thr Lys Gly Arg Val Lys Leu Ala Ala Val Asp Ala Thr Val
115 120 125

Asn Gln Val Leu Ala Ser Arg Tyr Gly Ile Arg Gly Phe Pro Thr Ile

130 135 140

Lys Ile Phe Gln Lys Gly Glu Ser Pro Val Asp Tyr Asp Gly Gly Arg
145 150 155 160

Thr Arg Ser Asp Ile Val Ser Arg Ala Leu Asp Trp Phe Ser Asp Asn
165 170 175

Ala

<210> 303
<211> 82
<212> PRT
<213> Homo sapien

<400> 303

Met Leu Thr Gln Ser Gln Gln Val Leu Arg Gly Ile Leu Val Phe Leu
1 5 10 15

Gln Asn Ile Leu Gln Glu Pro Ser Pro Ala Met Cys Phe Pro Lys Lys
20 25 30

Arg Ser Leu Trp Pro Asn Leu Arg Lys Gln Trp Ala Ser Ile His Ile
35 40 45

Asn Asp Pro Arg Gly Thr Leu Cys Pro Arg Cys Thr Gly Cys Asn Gln
50 55 60

Arg Gly Ser Gly Gly Ser Gly Leu Ile Trp Arg Asp Ser Phe Tyr His
65 70 75 80

His Pro

<210> 304
<211> 152
<212> PRT
<213> Homo sapien

<400> 304

Met Gly Phe Leu Pro Ala Ala His Pro Ser Gly Leu Gly Arg Gly Lys
1 5 10 15

Gly Glu Val Val Ala Met Gly Glu Val Arg Gly Glu Glu Gly Val Thr
20 25 30

Ala Arg Pro Pro Leu Gly Trp Ala Cys Asp Arg Val Leu Gly Arg Ser
35 40 45

Arg Ile Leu Ile Arg Ser Val Asn Gly Val Glu Ala Ala Leu Pro Arg
50 55 60

His Val Leu Pro Thr Thr His Gln Gln Ala Ser Val Ala Cys Arg Cys
65 70 75 80

Gln Gly Trp Val Gly Thr Leu Gly Gln Ala Gly Cys Leu Gly Gly Ala
85 90 95

Arg Gln Glu Pro Arg Gly Trp Leu Gln Gly Leu Pro Gly Gly Pro Gln
100 105 110

Gly Arg Gly Ala Gly Lys Arg Phe Gly Cys Leu Arg Arg Glu Val Val
115 120 125

Glu Thr Cys Leu Gln Val Arg Ala Val Ala Ser Ser Leu His His Leu
130 135 140

Ser Ala Tyr Gly Val Pro Asp Thr
145 150

<210> 305
<211> 42
<212> PRT
<213> Homo sapien

<400> 305

Met Thr Asn Arg Asn Ser Phe Thr Met Asn Cys Val His Val Leu Leu
1 5 10 15

Cys His Leu Phe Glu Asp Thr Ser Trp His Phe Leu Leu Cys Gln Met
20 25 30

Leu His Ser Leu Leu Asp Trp Gln Lys Arg
35 40

<210> 306
<211> 197
<212> PRT
<213> Homo sapien

<400> 306

Met Val Asp Leu Thr Gln Val Met Asp Asp Glu Val Phe Met Ala Phe
1 5 10 15

Ala Ser Tyr Ala Thr Ile Ile Leu Ser Lys Met Met Leu Met Ser Thr
20 25 30

Ala Thr Ala Phe Tyr Arg Leu Thr Arg Lys Val Phe Ala Asn Pro Glu
35 40 45

Asp Cys Val Ala Phe Gly Lys Gly Glu Asn Ala Lys Lys Tyr Leu Arg
50 55 60

Thr Asp Asp Arg Val Glu Arg Val Arg Ser His Cys Lys Ala Val Thr
65 70 75 80

Ile Ser Ile Phe Glu Arg Gln Ser Gln Asn Gly Ala Thr Asn Glu Val
85 90 95

Lys Ser Met Leu Tyr Arg Val Gln Gln Leu Lys Leu Ile His Thr His
100 105 110

Met Glu Gln Leu Thr Lys Asp Leu Arg Ala His Leu Asn Asp Leu Glu
115 120 125

Asn Ile Ile Pro Phe Leu Gly Ile Gly Leu Leu Tyr Ser Leu Ser Gly
130 135 140

Pro Asp Pro Ser Thr Ala Ile Leu His Phe Arg Leu Phe Val Gly Thr
145 150 155 160

Arg Ile Tyr His Thr Ile Ala Tyr Leu Thr Thr Pro Leu Arg Gln Gln
165 170 175

Ile Arg Ala Ser Val Phe Val Gly Tyr Gly Val Thr Leu Ser Met Ala
180 185 190

Tyr Arg Leu Leu Lys
195

<210> 307
<211> 146
<212> PRT
<213> Homo sapien

<400> 307

Gly Arg Cys Leu Arg Pro Ala Arg Ala Ala Thr Val Pro Ala Leu Arg
1 5 10 15

Ala Thr Arg Arg Arg Asp Arg Leu Ala Ala Ser Ser Ser Ser Ala Ser

20 25 30

Pro Phe Gln Thr Lys Ile Glu Lys Met Val Asp Leu Thr Gln Val Met
35 40 45

Asp Asp Glu Val Phe Met Ala Phe Ala Ser Tyr Ala Thr Ile Ile Leu
50 55 60

Ser Lys Met Met Leu Met Ser Thr Ala Thr Ala Phe Tyr Arg Leu Thr
65 70 75 80

Arg Lys Val Phe Ala Asn Pro Glu Asp Cys Val Ala Phe Gly Lys Gly
85 90 95

Glu Asn Ala Lys Lys Tyr Leu Arg Thr Asp Asp Arg Val Glu Arg Val
100 105 110

Arg Ser His Cys Lys Ala Val Thr Ile Ser Ile Phe Glu Arg Gln Ser
115 120 125

Gln Asn Gly Ala Thr Asn Glu Val Lys Ser Met Leu Tyr Arg Val Gln
130 135 140

Gln Leu
145

<210> 308
<211> 187
<212> PRT
<213> Homo sapien

<400> 308

Gly Arg Cys Leu Arg Pro Ala Arg Ala Ala Thr Val Pro Ala Leu Arg
1 5 10 15

Ala Thr Arg Arg Arg Asp Arg Leu Ala Ala Ser Ser Ser Ser Ala Ser
20 25 30

Pro Phe Gln Thr Lys Ile Glu Lys Met Val Asp Leu Thr Gln Val Met
35 40 45

Asp Asp Glu Val Phe Met Ala Phe Ala Ser Tyr Ala Thr Ile Ile Leu
50 55 60

Ser Lys Met Met Leu Met Ser Thr Ala Thr Ala Phe Tyr Arg Leu Thr
65 70 75 80

Arg Lys Val Phe Ala Asn Pro Glu Asp Cys Val Ala Phe Gly Lys Gly
85 90 95

Glu Asn Ala Lys Lys Tyr Leu Arg Thr Asp Asp Arg Val Glu Arg Val
100 105 110

Arg Arg Ala Gln Glu Ile Leu Gly Pro Glu Arg Gln Ile Gln Lys Asn
115 120 125

Leu His Val Asn Glu Thr Gly Val Glu Met Arg Met Ala Gly Asn Ala
130 135 140

Trp Lys Gln Thr Cys Asn Cys Leu Met Ala Trp Ser Ser Lys Ser Gln
145 150 155 160

Arg Met Glu Cys Asn Gly Met Ile Ser Ala His Arg Asn Leu Cys Leu
165 170 175

Pro Asp Ser Ser Asp Ser Pro Ala Ser Ala Ser
180 185

<210> 309
<211> 115
<212> PRT
<213> Homo sapien

<400> 309

Tyr Ser Cys Val Val Phe His Gly Val Tyr Val Pro His Cys Leu Tyr
1 5 10 15

Pro Ile His Ile Asp Gly His Leu Gly Cys Ile Ser Pro Phe Leu Ile
20 25 30

Leu Cys Glu Ser Leu Lys Pro Leu Pro Arg Phe Leu Gln Ile Pro Leu
35 40 45

Trp His Ile Ile Ser Arg Leu Thr Leu Asp Leu Gly Ser Cys Leu Tyr
50 55 60

Ala Cys Phe His Ile Leu Gln Leu Val Met Leu Asp Val Asn Pro Ala
65 70 75 80

Leu Ser Ser Val Pro Phe Lys Asn Glu Leu Lys Lys Met Trp Leu Lys
85 90 95

Ile Asp Leu Ser Lys Trp Lys Cys Arg Gly Val Tyr Thr Val Ala Ala

300

100 105 110

Gln Thr Phe
115

<210> 310
<211> 149
<212> PRT
<213> Homo sapien

<400> 310

Gly Arg Cys Leu Arg Pro Ala Arg Ala Ala Thr Val Pro Ala Leu Arg
1 5 10 15

Ala Thr Arg Arg Arg Asp Arg Leu Ala Ala Ser Ser Ser Ser Ala Ser
20 25 30

Pro Phe Gln Thr Lys Ile Glu Lys Met Val Asp Leu Thr Gln Val Met
35 40 45

Asp Asp Glu Val Phe Met Ala Phe Ala Ser Tyr Ala Thr Ile Ile Leu
50 55 60

Ser Lys Met Met Leu Met Ser Thr Ala Thr Ala Phe Tyr Arg Leu Thr
65 70 75 80

Arg Lys Val Phe Ala Asn Pro Glu Asp Cys Val Ala Phe Gly Lys Gly
85 90 95

Glu Asn Ala Lys Lys Tyr Leu Arg Thr Asp Asp Arg Val Glu Arg Val
100 105 110

Arg Ser Leu Glu Trp Ser Arg Pro Leu Tyr Ser His Pro Ala Leu Gln
115 120 125

Thr Ile Cys Arg Ser Thr Asp Leu Pro His His Cys Ile Phe Asp Thr
130 135 140

Pro Ser Pro Ala Lys
145

<210> 311
<211> 86
<212> PRT
<213> Homo sapien

<400> 311

Gly Arg Cys Leu Arg Pro Ala Arg Ala Ala Thr Val Pro Ala Leu Arg
1 5 10 15

Ala Thr Arg Arg Arg Asp Arg Leu Ala Ala Ser Ser Ser Ser Ala Ser
20 25 30

Pro Phe Gln Thr Lys Ile Glu Lys Met Val Asp Leu Thr Gln Val Met
35 40 45

Asp Asp Glu Val Phe Met Ala Phe Ala Ser Tyr Ala Thr Ile Ile Leu
50 55 60

Ser Lys Met Met Leu Met Ser Thr Ala Thr Ala Phe Tyr Arg Leu Thr
65 70 75 80

Arg Lys Ser Pro Pro Glu
85

<210> 312
<211> 114
<212> PRT
<213> Homo sapien

<400> 312

Gly Arg Cys Leu Arg Pro Ala Arg Ala Ala Thr Val Pro Ala Leu Arg
1 5 10 15

Ala Thr Arg Arg Arg Asp Arg Leu Ala Ala Ser Ser Ser Ser Ala Ser
20 25 30

Pro Ala His Leu Asn Asp Leu Glu Asn Ile Ile Pro Phe Leu Gly Ile
35 40 45

Gly Leu Leu Tyr Ser Leu Ser Gly Pro Asp Pro Ser Thr Ala Ile Leu
50 55 60

His Phe Arg Leu Phe Val Gly Ala Arg Ile Tyr His Thr Ile Ala Tyr
65 70 75 80

Leu Thr Pro Leu Pro Gln Pro Asn Arg Ala Leu Ser Phe Phe Val Gly
85 90 95

Tyr Gly Val Thr Leu Ser Met Ala Tyr Arg Leu Leu Lys Ser Lys Leu
100 105 110

Tyr Leu

<210> 313
<211> 145
<212> PRT
<213> Homo sapien

<400> 313

Ala Val Pro Ala Ser Gly Pro Arg Gly His Ser Pro Cys Ile Ala Arg
1 5 10 15

Asp Pro Ala Ala Gly Gln Ala Cys Cys Phe Leu Leu Leu Gly Leu Thr
20 25 30

Val Phe Ala Asn Pro Glu Asp Cys Val Ala Phe Gly Lys Gly Glu Asn
35 40 45

Ala Lys Lys Tyr Leu Arg Thr Asp Asp Arg Val Glu Arg Val Arg Arg
50 55 60

Ala His Leu Asn Asp Leu Glu Asn Ile Ile Pro Phe Leu Gly Ile Gly
65 70 75 80

Leu Leu Tyr Ser Leu Ser Gly Pro Asp Pro Ser Thr Ala Ile Leu His
85 90 95

Phe Arg Leu Phe Val Gly Ala Arg Ile Tyr His Thr Ile Ala Tyr Leu
100 105 110

Thr Pro Leu Pro Gln Pro Asn Arg Ala Leu Ser Phe Phe Val Gly Tyr
115 120 125

Gly Val Thr Leu Ser Met Ala Tyr Arg Leu Leu Lys Ser Lys Leu Tyr
130 135 140

Leu
145

<210> 314
<211> 530
<212> PRT
<213> Homo sapien

<400> 314

Pro Ser Asp His Arg Thr Gly Leu Gly Arg Asp Val Gly Ala Gly Ala
1 5 10 15

Arg Arg Ala Ala Arg Cys Arg Ala Glu Ala Ala Ala Ala Val Gly Thr

20 25 30

Ala Arg Ser Pro Ala Leu Gly Met Ala Leu Leu Val Leu Gly Leu Val
35 40 45

Ser Cys Thr Phe Phe Leu Ala Val Asn Gly Leu Tyr Ser Ser Ser Asp
50 55 60

Asp Val Ile Glu Leu Thr Pro Ser Asn Phe Asn Arg Glu Val Ile Gln
65 70 75 80

Ser Asp Ser Leu Trp Leu Val Glu Phe Tyr Ala Pro Trp Cys Gly His
85 90 95

Cys Gln Arg Leu Thr Pro Glu Trp Lys Lys Ala Ala Thr Ala Leu Lys
100 105 110

Asp Val Val Lys Val Gly Ala Val Asp Ala Asp Lys His His Ser Leu
115 120 125

Gly Gly Gln Tyr Gly Val Gln Gly Phe Pro Thr Ile Lys Ile Phe Gly
130 135 140

Ser Asn Lys Asn Arg Pro Glu Asp Tyr Gln Gly Gly Arg Thr Gly Glu
145 150 155 160

Ala Ile Val Asp Ala Ala Leu Ser Ala Leu Arg Gln Leu Val Lys Asp
165 170 175

Arg Leu Gly Gly Arg Ser Gly Gly Tyr Ser Ser Gly Lys Gln Gly Arg
180 185 190

Ser Asp Ser Ser Ser Lys Lys Asp Val Ile Glu Leu Thr Asp Asp Ser
195 200 205

Phe Asp Lys Asn Val Leu Asp Ser Glu Asp Val Trp Met Val Glu Phe
210 215 220

Tyr Ala Pro Trp Cys Gly His Cys Lys Asn Leu Glu Pro Glu Trp Ala
225 230 235 240

Ala Ala Ala Ser Glu Val Lys Glu Gln Thr Lys Gly Lys Val Lys Leu
245 250 255

Ala Ala Val Asp Ala Thr Val Asn Gln Val Leu Ala Ser Arg Tyr Gly
260 265 270

Ile Arg Gly Phe Pro Thr Ile Lys Ile Phe Gln Lys Gly Glu Ser Pro
275 280 285

Val Asp Tyr Asp Gly Gly Arg Thr Arg Ser Asp Ile Val Ser Arg Ala
290 295 300

Leu Asp Leu Phe Ser Asp Asn Ala Pro Pro Pro Glu Leu Leu Glu Ile
305 310 315 320

Ile Asn Glu Asp Ile Ala Lys Arg Thr Cys Glu Glu His Gln Leu Cys
325 330 335

Val Val Ala Val Leu Pro His Ile Leu Asp Thr Gly Ala Ala Gly Arg
340 345 350

Asn Ser Tyr Leu Glu Val Leu Leu Lys Leu Ala Asp Lys Tyr Lys Lys
355 360 365

Lys Met Trp Gly Trp Leu Trp Thr Glu Ala Gly Ala Gln Ser Glu Leu
370 375 380

Glu Thr Ala Leu Gly Ile Gly Gly Phe Gly Tyr Pro Ala Met Ala Ala
385 390 395 400

Ile Asn Ala Arg Lys Met Lys Phe Ala Leu Leu Lys Gly Ser Phe Ser
405 410 415

Glu Gln Gly Ile Asn Glu Phe Leu Arg Glu Leu Ser Phe Gly Arg Gly
420 425 430

Ser Thr Ala Pro Val Gly Gly Gly Ala Phe Pro Thr Ile Val Glu Arg
435 440 445

Glu Pro Trp Asp Gly Arg Asp Gly Glu Glu Cys Pro Gly Gly Lys Leu
450 455 460

Cys Gly Gln Gln Ser Trp Phe Thr Leu Leu Ser Leu Cys Ile Ser Ala
465 470 475 480

Pro Gly Val Lys Ser Phe Pro Ser Asp Leu Ser Pro Gly Ala Pro Val
485 490 495

Gly Leu Leu Arg Gly Ser Ser Leu Lys Thr Leu His Leu Pro Tyr His
500 505 510

Lys Phe Lys Cys Cys Met Ala Phe Asp Thr Leu Asp Ser Gln Asp Thr
515 520 525

Phe Gln
530

<210> 315
<211> 376
<212> PRT
<213> Homo sapien

<400> 315

Met Ala Asp Tyr Trp Lys Ser Gln Pro Lys Lys Phe Cys Asp Tyr Cys
1 5 10 15

Lys Cys Trp Ile Ala Asp Asn Arg Pro Ser Val Glu Phe His Glu Arg
20 25 30

Gly Lys Asn His Lys Glu Asn Val Ala Lys Arg Ile Ser Glu Ile Lys
35 40 45

Gln Lys Ser Leu Asp Lys Ala Lys Glu Glu Glu Lys Ala Ser Lys Glu
50 55 60

Phe Ala Ala Met Glu Ala Ala Ala Leu Lys Ala Tyr Gln Glu Asp Leu
65 70 75 80

Lys Arg Leu Gly Leu Glu Ser Glu Ile Leu Glu Pro Ser Ile Thr Pro
85 90 95

Val Thr Ser Thr Ile Pro Pro Thr Ser Thr Ser Asn Gln Gln Lys Glu
100 105 110

Lys Lys Asp Lys Lys Lys Arg Gln Lys Asp Pro Ser Lys Gly Arg Trp
115 120 125

Val Glu Gly Ile Thr Ser Glu Gly Tyr His Tyr Tyr Tyr Asp Leu Ile
130 135 140

Ser Gly Ala Ser Gln Trp Glu Lys Pro Glu Gly Phe Gln Gly Asp Leu
145 150 155 160

Lys Lys Thr Ala Val Lys Thr Val Trp Val Glu Gly Leu Ser Glu Asp
165 170 175

Gly Phe Thr Tyr Tyr Tyr Asn Thr Glu Thr Gly Glu Ser Arg Trp Glu

180 185 190

Lys Pro Asp Asp Phe Ile Pro His Thr Ser Asp Leu Pro Ser Ser Lys
195 200 205

Val Asn Glu Asn Ser Leu Gly Thr Leu Asp Glu Ser Lys Ser Ser Asp
210 215 220

Ser His Ser Asp Ser Asp Gly Glu Gln Glu Ala Glu Glu Gly Gly Val
225 230 235 240

Ser Thr Glu Thr Glu Lys Pro Lys Ile Lys Phe Gln Glu Lys Asn Lys
245 250 255

Asn Ser Asp Gly Gly Ser Asp Pro Glu Thr Gln Lys Glu Lys Ser Ile
260 265 270

Gln Lys Gln Asn Ser Leu Gly Ser Asn Glu Glu Lys Ser Lys Thr Leu
275 280 285

Lys Lys Ser Asn Pro Tyr Gly Glu Trp Gln Glu Ile Lys Gln Glu Val
290 295 300

Glu Ser His Glu Glu Val Asp Leu Glu Leu Pro Ser Thr Glu Asn Glu
305 310 315 320

Tyr Val Ser Thr Ser Glu Ala Asp Gly Gly Gly Glu Pro Lys Val Val
325 330 335

Phe Lys Glu Lys Thr Val Thr Ser Leu Gly Val Met Ala Asp Gly Val
340 345 350

Ala Pro Val Phe Lys Lys Arg Arg Thr Glu Asn Gly Lys Ser Arg Asn
355 360 365

Leu Arg Gln Arg Gly Asp Asp Gln
370 375

<210> 316
<211> 619
<212> PRT
<213> Homo sapien

<400> 316

Met Ala Ala Val Val Gln Gln Asn Asp Leu Val Phe Glu Phe Ala Ser
1 5 10 15

Asn Val Met Glu Asp Glu Arg Gln Leu Gly Asp Pro Ala Ile Phe Pro
20 25 30

Ala Val Ile Val Glu His Val Pro Gly Ala Asp Ile Leu Asn Ser Tyr
35 40 45

Ala Gly Leu Ala Cys Val Glu Glu Pro Ser Asp Met Ile Thr Glu Ser
50 55 60

Ser Leu Asp Val Ala Glu Glu Glu Ile Ile Asp Asp Asp Asp Asp Asp
65 70 75 80

Ile Thr Leu Thr Val Glu Ala Ser Cys His Asp Gly Asp Glu Thr Ile
85 90 95

Glu Thr Ile Glu Ala Ala Glu Ala Leu Leu Asn Met Asp Ser Pro Gly
100 105 110

Pro Met Leu Asp Glu Lys Arg Ile Asn Asn Asn Ile Phe Ser Ser Pro
115 120 125

Glu Asp Asp Met Val Val Ala Pro Val Thr His Val Ser Val Thr Leu
130 135 140

Asp Gly Ile Pro Glu Val Met Glu Thr Gln Gln Val Gln Glu Lys Tyr
145 150 155 160

Ala Asp Ser Pro Gly Ala Ser Ser Pro Glu Gln Pro Lys Arg Lys Lys
165 170 175

Gly Arg Lys Thr Lys Pro Pro Arg Pro Asp Ser Pro Ala Thr Thr Pro
180 185 190

Asn Ile Ser Val Lys Lys Lys Asn Lys Asp Gly Lys Gly Asn Thr Ile
195 200 205

Tyr Leu Trp Glu Phe Leu Leu Ala Leu Leu Gln Asp Lys Ala Thr Cys
210 215 220

Pro Lys Tyr Ile Lys Trp Thr Gln Arg Glu Lys Gly Ile Phe Lys Leu
225 230 235 240

Val Asp Ser Lys Ala Val Ser Arg Leu Trp Gly Lys His Lys Asn Lys
245 250 255

Pro Asp Met Asn Tyr Glu Thr Met Gly Arg Ala Leu Arg Tyr Tyr Tyr
260 265 270

Gln Arg Gly Ile Leu Ala Lys Val Glu Gly Gln Arg Leu Val Tyr Gln
275 280 285

Phe Lys Glu Met Pro Lys Asp Leu Ile Tyr Ile Asn Asp Glu Asp Pro
290 295 300

Ser Ser Ser Ile Glu Ser Ser Asp Pro Ser Leu Ser Ser Ser Ala Thr
305 310 315 320

Ser Asn Arg Asn Gln Thr Ser Arg Ser Arg Val Ser Ser Ser Pro Gly
325 330 335

Val Lys Gly Gly Ala Thr Ser Val Leu Lys Pro Gly Asn Ser Lys Ala
340 345 350

Ala Lys Pro Lys Asp Pro Val Glu Val Ala Gln Pro Ser Glu Val Leu
355 360 365

Arg Thr Val Gln Pro Thr Gln Ser Pro Tyr Pro Thr Gln Leu Phe Arg
370 375 380

Thr Val His Val Val Gln Pro Val Gln Ala Val Pro Glu Gly Glu Ala
385 390 395 400

Ala Arg Thr Ser Thr Met Gln Asp Glu Thr Leu Asn Ser Ser Val Gln
405 410 415

Ser Ile Arg Thr Ile Gln Ala Pro Thr Gln Val Pro Val Val Val Ser
420 425 430

Pro Arg Asn Gln Gln Leu His Thr Val Thr Leu Gln Thr Val Pro Leu
435 440 445

Thr Thr Val Ile Ala Ser Thr Asp Pro Ser Ala Gly Thr Gly Ser Gln
450 455 460

Lys Phe Ile Leu Gln Ala Ile Pro Ser Ser Gln Pro Met Thr Val Leu
465 470 475 480

Lys Glu Asn Val Met Leu Gln Ser Gln Lys Ala Gly Ser Pro Pro Ser
485 490 495

Ile Val Leu Gly Pro Ala Gln Val Gln Gln Val Leu Thr Ser Asn Val

500 505 510

Gln Thr Ile Cys Asn Gly Thr Val Ser Val Ala Ser Ser Pro Ser Phe
515 520 525

Ser Ala Thr Ala Pro Val Val Thr Phe Ser Pro Arg Ser Ser Gln Leu
530 535 540

Val Ala His Pro Pro Gly Thr Val Ile Thr Ser Val Ile Lys Thr Gln
545 550 555 560

Glu Thr Lys Thr Leu Thr Gln Glu Val Glu Lys Lys Glu Ser Glu Asp
565 570 575

His Leu Lys Glu Asn Thr Glu Lys Thr Glu Gln Gln Pro Gln Pro Tyr
580 585 590

Val Met Val Val Ser Ser Ser Asn Gly Phe Thr Ser Gln Val Ala Met
595 600 605

Lys Gln Asn Glu Leu Leu Glu Pro Asn Ser Phe
610 615

<210> 317
<211> 164
<212> PRT
<213> Homo sapien

<400> 317

Arg Ser Leu Ala Thr Arg Ser Ala Gly Pro Ala Val Ser Pro Leu Phe
1 5 10 15

Phe Phe Asn Ser Ala Arg Gly Pro Arg Pro Thr Gly Pro Gly Cys Ser
20 25 30

Ala Gly Gln Ser Ala Cys Gly Val Val Gly Lys Val Glu Ser Gly Asp
35 40 45

Val Ser Gly Asn Ser Cys Leu Arg Ser Gly Arg Arg Arg Arg Ala Glu
50 55 60

Leu Leu Gly Leu Glu Pro Ala Ser Leu Glu Gly Gly Trp Arg Phe Trp
65 70 75 80

Ala Pro Gly Glu Asp Thr Glu Thr Ala Gly Trp Arg Arg Asp Leu Arg
85 90 95

Leu Glu Ile Pro Ser Phe Ser Ser Gly Pro Val Ala Leu Leu Pro Leu
100 105 110

Pro Gly Asp Leu Asn Pro Phe Ile Pro Thr Pro Pro Leu Trp Ser Arg
115 120 125

Glu Tyr Arg Pro Cys Arg Gly Arg Gly Glu Glu Ala Ile Ser Asn Ala
130 135 140

Asp Trp Ile Val Trp Ala Pro Val Val Gly Asn Ser Gly Thr Leu Val
145 150 155 160

Pro Gly Thr Glu

<210> 318
<211> 361
<212> PRT
<213> Homo sapien

<400> 318

Met Glu Leu Glu Asp Gly Val Val Tyr Gln Glu Glu Pro Gly Gly Ser
1 5 10 15

Gly Ala Val Met Ser Glu Arg Val Ser Gly Leu Ala Gly Ser Ile Tyr
20 25 30

Arg Glu Phe Glu Arg Leu Ile Gly Arg Tyr Asp Glu Glu Val Val Lys
35 40 45

Glu Leu Met Pro Leu Val Val Ala Val Leu Glu Asn Leu Asp Ser Val
50 55 60

Phe Ala Gln Asp Gln Glu His Gln Val Glu Leu Glu Leu Leu Arg Asp
65 70 75 80

Asp Asn Glu Gln Leu Ile Thr Gln Tyr Glu Arg Glu Lys Ala Leu Arg
85 90 95

Lys His Ala Glu Glu Lys Phe Ile Glu Phe Glu Asp Ser Gln Glu Gln
100 105 110

Glu Lys Lys Asp Leu Gln Thr Arg Val Glu Ser Leu Glu Ser Gln Thr
115 120 125

Arg Gln Leu Glu Leu Lys Ala Lys Asn Tyr Ala Asp Gln Ser Leu Ser

130 135 140

Ala Val Cys Trp Gly Arg Arg Gln Gln Arg Trp Lys Val Phe Gln Thr
145 150 155 160

Trp Gln Arg Pro Ser Ile Ser Gly Val Ser Arg Leu Glu Glu Arg Glu
165 170 175

Ala Glu Leu Lys Lys Glu Tyr Asn Ala Leu His Gln Arg His Thr Glu
180 185 190

Met Ile His Asn Tyr Met Glu His Leu Glu Arg Thr Lys Leu His Gln
195 200 205

Leu Ser Gly Ser Asp Gln Leu Glu Ser Thr Ala His Ser Arg Ile Arg
210 215 220

Lys Glu Arg Pro Ile Ser Leu Gly Ile Phe Pro Leu Pro Ala Gly Asp
225 230 235 240

Gly Leu Leu Thr Pro Asp Ala Gln Lys Gly Gly Glu Thr Pro Gly Ser
245 250 255

Glu Gln Trp Lys Phe Gln Glu Leu Ser Gln Pro Arg Ser His Thr Ser
260 265 270

Leu Lys Asp Glu Leu Ser Asp Val Ser Gln Gly Gly Ser Lys Ala Thr
275 280 285

Thr Pro Ala Ser Thr Ala Asn Ser Asp Val Ala Thr Ile Pro Thr Asp
290 295 300

Thr Pro Leu Lys Glu Glu Asn Glu Gly Phe Val Lys Val Thr Asp Ala
305 310 315 320

Pro Asn Lys Ser Glu Ile Ser Lys His Ile Glu Val Gln Val Ala Gln
325 330 335

Glu Thr Arg Asn Val Ser Thr Gly Ser Ala Glu Asn Glu Glu Lys Ser
340 345 350

Val Asp Thr Phe Leu Val Ser Trp Ala
355 360

<210> 319
<211> 122

<212> PRT
<213> Homo sapien

<400> 319

Met Gly Gly Phe Lys Tyr Gly Asp Glu Gln Pro Arg Ser Asp Trp Arg
1 5 10 15

Ser Tyr Arg Arg Asn Leu Glu His Ala Val Leu Glu Leu Thr Leu Phe
20 25 30

Lys Thr Val Pro Ser Lys Met Glu Ile His Ser Ser Pro Phe Lys Cys
35 40 45

Ser Thr Ala Pro Pro Cys Asn Thr Ser Gly Gln Gly Lys Ile Thr Glu
50 55 60

His Ser Cys Glu Pro Asp Phe Cys Cys Leu Trp Ile Asp Lys Lys Gln
65 70 75 80

Asn Ser Phe Ser Ser Gly Val Gly Asn Arg Ser Leu Asp Ser Leu Leu
85 90 95

Ile Lys Gly Ser Ser Pro Phe Leu Val Leu Gly Val Arg Gly Ser Phe
100 105 110

Gly Lys Met His Pro Ser Ile Val Ala Phe
115 120

<210> 320
<211> 78
<212> PRT
<213> Homo sapien

<400> 320

Met Tyr Lys Gly Thr Ser Ile Thr Leu Gln Gln Gly Arg Arg Ser Gly
1 5 10 15

Ala Leu Gly Ser Leu Gly Thr Phe Ser Pro Ser Ala Gly Trp Pro Leu
20 25 30

Arg Leu Trp Leu Leu Cys Thr Leu Asn Phe Asp Leu Cys Pro Cys Gln
35 40 45

Gly Asp Arg Gly Gln Leu Gly Gln Gln Ala Ser Leu Lys Val Thr Pro
50 55 60

Glu Pro Leu Phe Ser Phe Thr Val Ala Met Gln Ala Arg Gly

65 70 75

<210> 321
<211> 92
<212> PRT
<213> Homo sapien

<400> 321

Val Pro Leu Ile Ile Phe Thr Ile Lys Ala Asn Ser Glu Ala Cys Arg
1 5 10 15

Asp Gly Leu Arg Ala Val Met Glu Cys Arg Asn Val Thr His Leu Leu
20 25 30

Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly Phe Gln Asp Val Glu Ala
35 40 45

Gln Ala Ala Thr Cys Asn His Thr Val Met Ala Leu Met Ala Ser Leu
50 55 60

Asp Ala Glu Lys Ala Gln Asp Ser Ser Ser Ala Ala Ala Pro Gln Leu
65 70 75 80

Leu Ile Val Leu Leu Gly Leu Ser Ala Leu Leu Gln
85 90

<210> 322
<211> 178
<212> PRT
<213> Homo sapien

<400> 322

Met Ala Ser Thr Ser Tyr Asp Tyr Cys Arg Val Pro Met Glu Asp Gly
1 5 10 15

Asp Lys Arg Cys Lys Leu Leu Leu Gly Ile Gly Ile Leu Val Leu Leu
20 25 30

Ile Ile Val Ile Leu Gly Val Pro Leu Ile Ile Phe Thr Ile Lys Ala
35 40 45

Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
50 55 60

Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
65 70 75 80

Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
85 90 95

Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
100 105 110

Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
115 120 125

Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu
130 135 140

Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
145 150 155 160

Ser Ser Ala Ala Ala Pro Gln Gln His Asn Gln Gln Leu Gly Arg Arg
165 170 175

Ser Cys

<210> 323
<211> 188
<212> PRT
<213> Homo sapien

<400> 323

Met Ala Ser Thr Ser Tyr Asp Tyr Cys Arg Val Pro Met Glu Asp Gly
1 5 10 15

Asp Lys Arg Cys Lys Leu Leu Leu Gly Ile Gly Ile Leu Val Leu Leu
20 25 30

Ile Ile Val Ile Leu Gly Val Pro Leu Ile Ile Phe Thr Ile Lys Ala
35 40 45

Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
50 55 60

Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
65 70 75 80

Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
85 90 95

Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
100 105 110

```
Val Glu Glu Leu Glu Val Thr Thr Leu Asn His Lys Leu Gln Asp Ala
        115                 120                 125

Ser Arg Pro Gly Phe Leu Phe Ser Val Ala Pro Pro Leu Gln Thr Arg
    130                 135                 140

Leu Arg Arg Glu Asn Gln Val Leu Ser Val Arg Ile Ala Asp Lys Lys
145                 150                 155                 160

Tyr Tyr Pro Ser Ser Gln Asp Ser Ser Ser Ala Ala Ala Pro Gln Leu
                165                 170                 175

Leu Ile Val Leu Leu Gly Leu Ser Ala Leu Leu Gln
            180                 185


<210>  324
<211>  108
<212>  PRT
<213>  Homo sapien

<400>  324

Leu Arg Ser Leu Glu Arg Glu Ala Ala Gly Glu Gly Thr Gly Arg Arg
1               5                   10                  15

Gly Glu Gly Pro Trp Gly Arg Arg Glu Asn Pro Val Arg Arg Met Pro
            20                  25                  30

Trp Ile Gly Gly Gly Leu Ile Ala Val Trp Gly Gly Ala Ile Asn Gly
        35                  40                  45

Gly Gly Ser Ile Asp Gly Gly Glu Gly Leu Met Asp Gly Trp Gly Gly
    50                  55                  60

Ser Ser Asp Gly Gly Gly Ala Trp Gly Arg Ala Trp Ser Gly Ala Ser
65                  70                  75                  80

Ala Cys Cys Leu Gln Ser Ala Leu Ser Pro Ser Ser Gly Pro Leu Gly
                85                  90                  95

Thr Ser Trp Lys Val Arg Pro Ala Arg Leu Phe Ala
            100                 105


<210>  325
<211>  250
<212>  PRT
<213>  Homo sapien
```

<400> 325

His Pro Val Thr Cys Ile Tyr Met Gln Ile Tyr Trp Phe Met Gln Asn
1 5 10 15

Ser Gly Gly Leu Gly Gly Gly Phe Phe Ser Leu Lys Leu Val Gln Ser
20 25 30

Leu Lys Lys Arg Arg Lys Ala Val Ser Gly Val Leu His Val Arg Leu
35 40 45

Ala Pro Gly Ser Trp Ala Gly Ser Arg Arg Thr Lys Thr Glu Leu Ala
50 55 60

Arg Leu Ala Glu Lys Gly Glu Gln Arg Pro Tyr Thr Glu Ser Ser Gly
65 70 75 80

Ala Pro Thr Lys Ser Arg Met Pro Thr Pro Ala Ser Arg Ser Thr Pro
85 90 95

Lys Ala Gly Gly Glu Ala Glu Cys Ala Ser Ala Ile Arg Arg Arg Arg
100 105 110

Leu Leu Pro Leu Arg Arg Glu His Ala Gly Pro Lys Met Ala Ala Ser
115 120 125

Arg Tyr Arg Arg Phe Leu Lys Leu Cys Glu Glu Trp Pro Val Asp Glu
130 135 140

Thr Lys Arg Gly Arg Asp Leu Gly Ala Tyr Leu Arg Gln Arg Val Ala
145 150 155 160

Gln Ala Phe Arg Glu Gly Glu Asn Thr Gln Val Ala Glu Pro Glu Ala
165 170 175

Cys Asp Gln Met Tyr Glu Ser Leu Ala Arg Leu His Ser Asn Tyr Tyr
180 185 190

Lys His Lys Tyr Pro Arg Pro Arg Asp Thr Ser Phe Ser Gly Leu Ser
195 200 205

Leu Glu Glu Tyr Lys Leu Ile Leu Ser Thr Asp Thr Leu Glu Glu Leu
210 215 220

Lys Glu Ile Asp Lys Gly Met Trp Lys Lys Leu Gln Glu Lys Phe Ala
225 230 235 240

Pro Lys Gly Pro Glu Glu Asp His Lys Ala
245 250

<210> 326
<211> 68
<212> PRT
<213> Homo sapien

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> x=any amino acid

<400> 326

Xaa Leu Asp Arg Glu Gln Pro Leu Gly Ser Arg Thr Gln Tyr Pro Arg
1 5 10 15

Pro Arg Asp Thr Ser Phe Ser Gly Leu Ser Leu Glu Glu Tyr Lys Leu
20 25 30

Ile Leu Ser Thr Asp Thr Leu Glu Glu Leu Lys Glu Ile Asp Lys Gly
35 40 45

Met Trp Lys Lys Leu Gln Glu Lys Phe Ala Pro Lys Gly Pro Glu Glu
50 55 60

Asp His Lys Ala
65

<210> 327
<211> 221
<212> PRT
<213> Homo sapien

<400> 327

Met Met Gly Ser Asp Ser Gly Pro Arg Pro Ser Pro Ser Gln Cys Leu
1 5 10 15

Leu Asn Ser Thr Ala Cys Ala Glu Ser Thr His Gln Asp Ser Asn Pro
20 25 30

Cys Ser Thr Ser Gln Leu Cys Asn Leu Ser Lys Leu Leu His Cys Leu
35 40 45

Leu Pro Gln Phe Pro His Leu Lys Thr Gly Asp Arg Lys Gly Cys Val
50 55 60

```
Glu Gln Ala Lys Phe Cys Asp Glu Ala Ser Gly Ser Val Gly Cys Thr
65                  70                  75                  80

Ala Asp Ser Ala Gly Pro Phe Leu Cys Pro His Thr Glu Gln Gly Asn
                85                  90                  95

Glu Gln His Ile Pro Ala Leu Met Pro Arg Val Arg Arg Gly Gln Glu
            100                 105                 110

Thr Thr Asp Ser Val Leu Gly Thr Glu Ser Gly Thr Gln Cys Ser Val
        115                 120                 125

Pro Ala Ser Gly His Phe Cys Tyr Leu Phe Asp Leu Leu Phe Arg Ser
    130                 135                 140

Trp Val Ser Thr Phe Phe Arg Asn Thr Leu Cys Glu Lys Gln Ala Met
145                 150                 155                 160

Leu Val Ser Gly Lys Pro Ser Gly Ser Asn Leu Cys His Gln Val Leu
                165                 170                 175

Asp Phe Ser Pro Ser Leu Phe Leu Ser Ser Pro Phe Ala Asp Thr Leu
            180                 185                 190

Glu Glu Leu Lys Glu Ile Asp Lys Gly Met Trp Lys Lys Leu Gln Glu
        195                 200                 205

Lys Phe Ala Pro Lys Gly Pro Glu Glu Asp His Lys Ala
    210                 215                 220
```

<210> 328
<211> 108
<212> PRT
<213> Homo sapien

<400> 328

```
Met Val Ile Ile Cys Cys Leu Gly Ala Pro Arg Thr Gln Pro Phe Gln
1               5                   10                  15

Ala Gln Leu Pro Asn Leu Ser Ala Lys Leu Leu Ala Phe Pro Ser Thr
            20                  25                  30

Leu Ser Thr Pro Pro Val Ser Glu Leu Glu Ser Ala Leu Gln Met Glu
        35                  40                  45

Pro Ala Ala Phe Gln Ala Leu Tyr Ser Ala Glu Lys Pro Lys Leu Glu
```

50 55 60

Asp Glu His Leu Val Phe Phe Cys Gln Met Gly Lys Arg Gly Leu Gln
65 70 75 80

Ala Thr Gln Leu Ala Arg Ser Leu Gly Tyr Thr Gly Ala Arg Asn Tyr
85 90 95

Ala Gly Ala Tyr Arg Glu Trp Leu Glu Lys Glu Ser
100 105

<210> 329
<211> 172
<212> PRT
<213> Homo sapien

<400> 329

Gly Lys Ala Leu Cys His Pro Gln Ile Ala Met Ala Gln Val Pro Pro
1 5 10 15

Gly Thr Pro Arg Arg Gly Leu Pro Arg His Gln Gly Leu Gly His Ala
20 25 30

Thr His Leu His Gln Ala Val Phe Cys Trp Val Ala Glu Gly Met Arg
35 40 45

Ala Asp Thr Thr Cys Ser Pro Arg Val Ala Val Gly Thr Ala Ala Glu
50 55 60

Gly Leu Leu Leu Arg Val His Met Trp Gly Lys Glu Met Leu Gln Ala
65 70 75 80

Pro Arg Gly Arg Ala Arg Ala Ala Leu Arg Arg Leu Ala Val Ala Thr
85 90 95

Arg Thr Met Ala Gly Val Ser Glu Leu Glu Ser Ala Leu Gln Met Glu
100 105 110

Pro Ala Ala Phe Gln Ala Leu Tyr Ser Ala Glu Lys Pro Lys Leu Glu
115 120 125

Asp Glu His Leu Val Phe Phe Cys Gln Met Gly Lys Arg Gly Leu Gln
130 135 140

Ala Thr Gln Leu Ala Arg Ser Leu Gly Tyr Thr Gly Ala Arg Asn Tyr
145 150 155 160

Ala Gly Ala Tyr Arg Glu Trp Leu Glu Lys Glu Ser
165 170

<210> 330
<211> 335
<212> PRT
<213> Homo sapien

<400> 330

Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile
1 5 10 15

Leu Ala Ile Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His
20 25 30

Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu
35 40 45

Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe
50 55 60

Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr
65 70 75 80

Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe
85 90 95

Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser
100 105 110

Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val
115 120 125

Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr
130 135 140

Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro
145 150 155 160

Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn
165 170 175

Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro
180 185 190

Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly

195 200 205

Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser
210 215 220

Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val
225 230 235 240

Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly
245 250 255

Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Ser
260 265 270

Ala Pro Arg Gly Ser Pro Leu Tyr Cys Pro His Pro Arg Ala Trp His
275 280 285

Gly Cys His Leu Ser Thr Asp Pro Asp Thr Val Leu Met Cys Val Gly
290 295 300

Val Val Pro Trp Gly Thr Leu Ile Thr His Leu Thr Pro Arg Ala Gly
305 310 315 320

Gly Leu Pro Leu His Leu Pro Lys Pro Cys Cys Leu Leu Ser Cys
325 330 335

<210> 331
<211> 351
<212> PRT
<213> Homo sapien

<400> 331

Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile
1 5 10 15

Leu Ala Ile Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His
20 25 30

Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Arg Glu Leu Gly
35 40 45

Gly Ala Met Glu Gly Val Arg Val Ser Ser Cys Arg Pro Pro Gly Asp
50 55 60

Leu Glu Ser Thr Gln Pro Ser Leu Gln Phe Gly Ala Val Pro His Leu
65 70 75 80

```
Val Tyr Leu Leu Leu Phe Phe Leu Arg Leu Ile Leu Thr Leu Ser Ala
                85                  90                  95

Ala Val Lys Leu Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val
            100                 105                 110

Glu Trp Lys Phe Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn
        115                 120                 125

Asn Lys Ile Thr Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr
    130                 135                 140

Gly Ile Thr Phe Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr
145                 150                 155                 160

Cys Met Val Ser Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val
                165                 170                 175

Lys Leu Ile Val Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro
            180                 185                 190

Ser Ser Ala Thr Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln
        195                 200                 205

Asp Gly Ser Pro Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val
    210                 215                 220

Met Pro Thr Asn Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr
225                 230                 235                 240

Val Leu Asn Pro Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala
                245                 250                 255

Ser Asp Thr Gly Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr
            260                 265                 270

Pro Met Thr Ser Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val
        275                 280                 285

Gly Val Ile Val Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile
    290                 295                 300

Leu Val Phe Gly Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg
305                 310                 315                 320
```

Thr Lys Lys Gly Thr Ser Ser Lys Lys Val Ile Tyr Ser Gln Pro Ser
325 330 335

Ala Arg Ser Glu Gly Glu Phe Lys Gln Thr Ser Ser Phe Leu Val
340 345 350

<210> 332
<211> 250
<212> PRT
<213> Homo sapien

<400> 332

Lys Gly Ala Ser Ala Pro Arg Arg Gly Val Ala Ala Gly Phe His Leu
1 5 10 15

Ala Ala Gly Leu Ser Val Leu Lys Ser Ser Gly Ser Leu His Gln Ser
20 25 30

Glu Arg Ala Gly Val Gly Ser Trp Pro Ile Arg Arg Gly Gly Arg Gly
35 40 45

Arg Ala Gly Phe His Leu Ala Ala Gly Ser Gln Ser Pro Arg Cys Ser
50 55 60

Arg Gly Ala Val Ser Val Pro Arg Ser Pro Ser Ala Ala Val Val Ser
65 70 75 80

Val Ser Leu Ile Ala Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu
85 90 95

Leu Cys Leu Phe Ile Leu Ala Ile Leu Leu Cys Lys Phe Pro Glu Phe
100 105 110

Arg Glu Glu Ser Val Gly Arg Val Arg Gly Trp Arg Lys Ala Leu Pro
115 120 125

Thr Pro Leu Ala Arg Gly Arg Gly Gly Ala Gln Lys Pro Ser Tyr Ile
130 135 140

Val Leu Arg Ile Ile Phe Ser Thr Pro Gly Trp Ser Leu Phe His His
145 150 155 160

Ser His Ser Trp Val Ser Gly Trp Leu Pro Ser Pro Thr Leu Val Ser
165 170 175

Cys Asp Arg Thr Pro His Gly His Gln Glu Gly Ala Asp Pro Ser Ala
180 185 190

His Thr Arg Gly Thr Leu Leu Val Leu Thr Gly Glu Gly Arg Arg Ala
195 200 205

Lys Asp Pro Ser Thr Leu Ile Tyr Pro Ala Arg Ala Pro His Ala Pro
210 215 220

Gly Lys Gly Gln Pro Ala Pro Pro Thr Ala Thr Gln His Pro Arg Thr
225 230 235 240

Pro Leu Arg Ser Arg Glu Pro Trp Leu Leu
245 250

<210> 333
<211> 66
<212> PRT
<213> Homo sapien

<400> 333

Pro Val Ser Glu Leu Glu Ser Ala Leu Gln Met Glu Pro Ala Ala Phe
1 5 10 15

Gln Ala Leu Tyr Ser Ala Glu Lys Pro Lys Leu Glu Asp Glu His Leu
20 25 30

Val Phe Phe Cys Gln Met Gly Lys Arg Gly Leu Gln Ala Thr Gln Leu
35 40 45

Ala Arg Ser Leu Gly Tyr Thr Gly Tyr Gly Glu Val Trp Leu Leu Ala
50 55 60

Gly Arg
65

<210> 334
<211> 113
<212> PRT
<213> Homo sapien

<400> 334

Gly Asp Ser Glu Asp Pro Arg Phe Asp Pro Asp Gly Pro Gly Ser Ser
1 5 10 15

Thr Cys Ala Leu Ala Arg Arg Arg Gln Leu Gly Pro Ser Gln Gly Arg
20 25 30

Ser Thr Ser Arg Cys Pro Ser Trp Arg Val Leu Cys Arg Trp Ser Gln

35 40 45

Leu Pro Ser Arg Leu Tyr Ile Leu Leu Arg Ser Gln Ser Trp Lys Met
50 55 60

Ser Ile Ser Phe Ser Ser Val Arg Trp Ala Ser Gly Ala Ser Arg Pro
65 70 75 80

Arg Ser Trp Pro Gly Val Leu Asp Thr Leu Gly Leu Ala Thr Thr Leu
85 90 95

Glu Pro Ile Glu Asn Gly Trp Arg Lys Arg Val Arg Gln Glu Ala Ala
100 105 110

Tyr

<210> 335
<211> 220
<212> PRT
<213> Homo sapien

<400> 335

Gly Lys Ala Leu Cys His Pro Gln Ile Ala Met Ala Gln Val Pro Pro
1 5 10 15

Gly Thr Pro Arg Arg Gly Leu Pro Arg His Gln Gly Leu Gly His Ala
20 25 30

Thr His Leu His Gln Ala Val Phe Cys Trp Val Ala Glu Gly Met Arg
35 40 45

Ala Asp Thr Thr Cys Ser Pro Arg Val Ala Val Gly Thr Ala Ala Glu
50 55 60

Gly Leu Leu Leu Arg Val His Met Trp Gly Lys Glu Met Leu Gln Ala
65 70 75 80

Pro Arg Gly Arg Ala Arg Ala Ala Leu Arg Arg Leu Ala Val Ala Thr
85 90 95

Arg Thr Met Ala Gly Gly Cys Arg Ala Pro Ser Ser Ala Pro Thr Val
100 105 110

Ser Leu Pro Glu Leu Arg Ser Leu Leu Ala Ser Gly Arg Ala Arg Leu
115 120 125

Phe Asp Val Arg Ser Arg Glu Glu Ala Ala Ala Gly Thr Ile Pro Gly
130 135 140

Ala Leu Asn Ile Pro Val Ser Glu Leu Glu Ser Ala Leu Gln Met Glu
145 150 155 160

Pro Ala Ala Phe Gln Ala Leu Tyr Ser Ala Glu Lys Pro Lys Leu Glu
165 170 175

Asp Glu His Leu Val Phe Phe Cys Gln Met Gly Lys Arg Gly Leu Gln
180 185 190

Ala Thr Gln Leu Ala Arg Ser Leu Gly Tyr Thr Gly Ala Arg Asn Tyr
195 200 205

Ala Gly Ala Tyr Arg Glu Trp Leu Glu Lys Glu Ser
210 215 220

<210> 336
<211> 199
<212> PRT
<213> Homo sapien

<400> 336

Gly Lys Ala Leu Cys His Pro Gln Ile Ala Met Ala Gln Val Pro Pro
1 5 10 15

Gly Thr Pro Arg Arg Gly Leu Pro Arg His Gln Gly Leu Gly His Ala
20 25 30

Thr His Leu His Gln Ala Val Phe Cys Trp Val Ala Glu Gly Met Arg
35 40 45

Ala Asp Thr Thr Cys Ser Pro Arg Val Ala Val Gly Thr Ala Ala Glu
50 55 60

Gly Leu Leu Leu Arg Val His Met Trp Gly Lys Glu Met Leu Gln Ala
65 70 75 80

Pro Arg Gly Arg Ala Arg Ala Ala Leu Arg Arg Leu Ala Val Ala Thr
85 90 95

Arg Thr Met Ala Gly Ala Gly Arg Ala Arg Leu Phe Asp Val Arg Ser
100 105 110

Arg Glu Glu Ala Ala Ala Gly Thr Ile Pro Gly Ala Leu Asn Ile Pro

115 120 125

Val Ser Glu Leu Glu Ser Ala Leu Gln Met Glu Pro Ala Ala Phe Gln
130 135 140

Ala Leu Tyr Ser Ala Glu Lys Pro Lys Leu Glu Asp Glu His Leu Val
145 150 155 160

Phe Phe Cys Gln Met Gly Lys Arg Gly Leu Gln Ala Thr Gln Leu Ala
165 170 175

Arg Ser Leu Gly Tyr Thr Gly Ala Arg Asn Tyr Ala Gly Ala Tyr Arg
180 185 190

Glu Trp Leu Glu Lys Glu Ser
195

<210> 337
<211> 105
<212> PRT
<213> Homo sapien

<400> 337

Met Leu Gln Ala Pro Arg Gly Pro Gly Arg Ala Arg Leu Phe Asp Val
1 5 10 15

Arg Ser Arg Glu Glu Ala Ala Ala Gly Thr Ile Pro Gly Ala Leu Asn
20 25 30

Ile Pro Val Ser Glu Leu Glu Ser Ala Leu Gln Met Glu Pro Ala Ala
35 40 45

Phe Gln Ala Leu Tyr Ser Ala Glu Lys Pro Lys Leu Glu Asp Glu His
50 55 60

Leu Val Phe Phe Cys Gln Met Gly Lys Arg Gly Leu Gln Ala Thr Gln
65 70 75 80

Leu Ala Arg Ser Leu Gly Tyr Thr Gly Ala Arg Asn Tyr Ala Gly Ala
85 90 95

Tyr Arg Glu Trp Leu Glu Lys Glu Ser
100 105

<210> 338
<211> 131
<212> PRT

<213> Homo sapien

<400> 338

Met Ala Ala Val Thr Pro Arg Pro Pro Leu Pro Glu Gly Cys Arg Ala
1 5 10 15

Pro Ser Ser Ala Pro Thr Val Ser Leu Pro Glu Leu Arg Ser Leu Leu
20 25 30

Ala Ser Gly Arg Ala Arg Leu Phe Asp Val Arg Ser Arg Glu Glu Ala
35 40 45

Ala Ala Gly Thr Ile Pro Gly Ala Leu Asn Ile Pro Val Ser Glu Leu
50 55 60

Glu Ser Ala Leu Gln Met Glu Pro Ala Ala Phe Gln Ala Leu Tyr Ser
65 70 75 80

Ala Glu Lys Pro Lys Leu Glu Asp Glu His Leu Val Phe Phe Cys Gln
85 90 95

Met Gly Lys Arg Gly Leu Gln Ala Thr Gln Leu Ala Arg Ser Leu Gly
100 105 110

Tyr Thr Gly Ala Arg Asn Tyr Ala Gly Ala Tyr Arg Glu Trp Leu Glu
115 120 125

Lys Glu Ser
130

<210> 339
<211> 134
<212> PRT
<213> Homo sapien

<400> 339

Met Glu Gly Gly Val Arg Glu Arg Glu Gly Ala Ala Ala His Pro Val
1 5 10 15

Leu Pro Thr Pro Gln Phe Ile Gly Thr Ala Ser Leu Ile Val Cys Val
20 25 30

Leu Ala Ile Val Asp Pro Tyr Asn Asn Pro Val Pro Arg Gly Leu Glu
35 40 45

Ala Phe Thr Val Gly Leu Val Val Leu Val Ile Gly Thr Ser Met Gly
50 55 60

Phe Asn Ser Gly Tyr Ala Val Asn Pro Ala Arg Asp Phe Gly Pro Arg
65 70 75 80

Leu Phe Thr Ala Leu Ala Gly Trp Gly Ser Ala Val Phe Thr Thr Gly
85 90 95

Gln His Trp Trp Trp Val Pro Ile Val Ser Pro Leu Leu Gly Ser Ile
100 105 110

Ala Gly Val Phe Val Tyr Gln Leu Met Ile Gly Cys His Leu Glu Gln
115 120 125

Pro Pro Pro Ser Asn Glu
130

<210> 340
<211> 76
<212> PRT
<213> Homo sapien

<400> 340

Gln Phe Ile Gly Thr Ala Ser Leu Ile Val Cys Val Leu Ala Ile Val
1 5 10 15

Asp Pro Tyr Asn Asn Pro Val Pro Arg Gly Leu Glu Ala Phe Thr Val
20 25 30

Gly Leu Val Val Leu Val Ile Gly Thr Ser Met Gly Phe Asn Ser Gly
35 40 45

Tyr Ala Val Asn Pro Ala Arg Asp Phe Gly Pro Arg Leu Phe Thr Ala
50 55 60

Leu Ala Gly Trp Gly Ser Ala Val Phe Thr Thr Gly
65 70 75

<210> 341
<211> 367
<212> PRT
<213> Homo sapien

<400> 341

Pro Pro Ala Leu Glu Ala Ala Ala Arg Cys Ala Thr Ala Ser Arg His
1 5 10 15

Pro Cys Pro Pro Asp Ser Ala Ala Ala Cys Pro Ala Met Gly Arg Gln

```
            20                  25                  30

Lys Glu Leu Val Ser Arg Cys Gly Glu Met Leu His Ile Arg Tyr Arg
        35                  40                  45

Leu Leu Arg Gln Ala Leu Ala Glu Cys Leu Gly Thr Leu Ile Leu Val
    50                  55                  60

Met Phe Gly Cys Gly Ser Val Ala Gln Val Val Leu Ser Arg Gly Thr
65                  70                  75                  80

His Gly Gly Phe Leu Thr Ile Asn Leu Ala Phe Gly Phe Ala Val Thr
                85                  90                  95

Leu Gly Ile Leu Ile Ala Gly Gln Val Ser Gly Ala His Leu Asn Pro
            100                 105                 110

Ala Val Thr Phe Ala Met Cys Phe Leu Ala Arg Glu Pro Trp Ile Lys
        115                 120                 125

Leu Pro Ile Tyr Thr Leu Ala Gln Thr Leu Gly Ala Phe Leu Gly Ala
    130                 135                 140

Gly Ile Val Phe Gly Leu Tyr Tyr Gly Lys His Ser Pro Pro Cys Pro
145                 150                 155                 160

Pro Pro Leu Pro Pro Ser Leu Cys Ser Gly Pro Ala Gly Thr Arg Pro
                165                 170                 175

Phe Asp Asp Arg Arg Leu Asp Leu Pro Arg Pro Arg Ala His Asp Ser
            180                 185                 190

Leu Ile His Ala Gln Gly Gln Asp Ala Ile Trp His Phe Ala Asp Asn
        195                 200                 205

Gln Leu Phe Val Ser Gly Pro Asn Gly Thr Ala Gly Ile Phe Ala Thr
    210                 215                 220

Tyr Pro Ser Gly His Leu Asp Met Ile Asn Gly Phe Phe Asp Gln Phe
225                 230                 235                 240

Ile Gly Thr Ala Ser Leu Ile Val Cys Val Leu Ala Ile Val Asp Pro
                245                 250                 255

Tyr Asn Asn Pro Val Pro Arg Gly Leu Glu Ala Phe Thr Val Gly Leu
            260                 265                 270
```

Val Val Leu Val Ile Gly Thr Ser Met Gly Phe Asn Ser Gly Tyr Ala
275 280 285

Val Asn Pro Ala Arg Asp Phe Gly Pro Arg Leu Phe Thr Ala Leu Ala
290 295 300

Gly Trp Gly Ser Ala Val Phe Thr Thr Gly Gln His Trp Trp Trp Val
305 310 315 320

Pro Ile Val Ser Pro Leu Leu Gly Ser Ile Ala Gly Val Phe Val Tyr
325 330 335

Gln Leu Met Ile Gly Cys His Leu Glu Gln Pro Pro Pro Ser Asn Glu
340 345 350

Glu Glu Asn Val Lys Leu Ala His Val Lys His Lys Glu Gln Ile
355 360 365

<210> 342
<211> 214
<212> PRT
<213> Homo sapien

<400> 342

Ala Thr Pro Ser Ala Cys Cys Asn Thr Ala Val Leu Leu Leu Thr His
1 5 10 15

Asn Ser Trp Glu Gly Gly Glu Gly Thr Pro Glu Arg Glu Val Trp Ala
20 25 30

Gln Ala Ser Pro Pro Thr His Cys Val Ser Asn Leu Ser Pro Asp Ala
35 40 45

Ile Trp His Phe Ala Asp Asn Gln Leu Phe Val Ser Gly Pro Asn Gly
50 55 60

Thr Ala Gly Ile Phe Ala Thr Tyr Pro Ser Gly His Leu Asp Met Ile
65 70 75 80

Asn Gly Phe Phe Asp Gln Phe Ile Gly Thr Ala Ser Leu Ile Val Cys
85 90 95

Val Leu Ala Ile Val Asp Pro Tyr Asn Asn Pro Val Pro Arg Gly Leu
100 105 110

Glu Ala Phe Thr Val Gly Leu Val Val Leu Val Ile Gly Thr Ser Met
115 120 125

Gly Phe Asn Ser Gly Tyr Ala Val Asn Pro Ala Arg Asp Phe Gly Pro
130 135 140

Arg Leu Phe Thr Ala Leu Ala Gly Trp Gly Ser Ala Val Phe Thr Thr
145 150 155 160

Gly Gln His Trp Trp Trp Val Pro Ile Val Ser Pro Leu Leu Gly Ser
165 170 175

Ile Ala Gly Val Phe Val Tyr Gln Leu Met Ile Gly Cys His Leu Glu
180 185 190

Gln Pro Pro Pro Ser Asn Glu Glu Glu Asn Val Lys Leu Ala His Val
195 200 205

Lys His Lys Glu Gln Ile
210

<210> 343
<211> 105
<212> PRT
<213> Homo sapien

<400> 343

Met Ala Lys Ile Ser Ser Pro Thr Glu Thr Glu Arg Cys Ile Glu Ser
1 5 10 15

Leu Ile Ala Val Phe Gln Lys Tyr Ala Gly Lys Asp Gly Tyr Asn Tyr
20 25 30

Thr Leu Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Thr Glu Leu Ala
35 40 45

Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu Asp Arg Met Met
50 55 60

Lys Lys Leu Asp Thr Asn Ser Asp Gly Gln Leu Asp Phe Ser Glu Phe
65 70 75 80

Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu
85 90 95

Lys Ala Val Pro Ser Gln Lys Arg Thr
100 105

<210> 344
<211> 222
<212> PRT
<213> Homo sapien

<400> 344

Gly Leu Glu Phe Glu Arg Trp Leu Asn Ala Thr Gly Pro Pro Leu Ala
1 5 10 15

Glu Pro Asp Leu Ser Gln Gly Ser Ser Leu Thr Arg Pro Val Glu Ala
20 25 30

Leu Phe Gln Leu Trp Thr Ala Glu Pro Leu Asp His Ala Ala Ala Ser
35 40 45

Ala Ser Ala Ile Asp Ile Ser Lys Trp Arg Thr Phe Gln Thr Ala Leu
50 55 60

Phe Leu Asp Arg Leu Leu Asp Gly Ser Pro Leu Pro Gln Glu Val Val
65 70 75 80

Met Ser Leu Ser Lys Cys Tyr Ser Ser Leu Leu Asp Ser Met Asn Ala
85 90 95

Glu Ile Arg Ile Arg Trp Leu Gln Ile Val Val Arg Asn Asp Tyr Tyr
100 105 110

Pro Asp Leu His Arg Val Arg Arg Phe Leu Glu Ser Gln Met Ser Arg
115 120 125

Met Tyr Thr Ile Pro Leu Tyr Glu Asp Leu Cys Thr Gly Ala Leu Lys
130 135 140

Ser Phe Ala Leu Glu Val Phe Tyr Gln Thr Gln Gly Arg Leu His Pro
145 150 155 160

Asn Leu Arg Arg Ala Ile Gln Gln Ile Leu Ser Gln Gly Leu Gly Ser
165 170 175

Ser Thr Glu Pro Ala Ser Glu Pro Ser Thr Glu Leu Gly Lys Ala Glu
180 185 190

Ala Asp Thr Asp Ser Asp Ala Gln Ala Leu Leu Leu Gly Asp Glu Ala
195 200 205

Pro Ser Ser Ala Ile Ser Leu Arg Asp Val Asn Val Ser Ala
210 215 220

<210> 345
<211> 450
<212> PRT
<213> Homo sapien

<400> 345

Glu Leu Thr Ala Gly Ala Gly Leu Ile Pro Ala Gly Trp Lys Val Gly
1 5 10 15

Cys Gly Cys Ala Gly Trp Glu Ser Glu Pro Arg Gly Leu Pro Pro Ser
20 25 30

Pro Pro Ser Arg Cys Arg Tyr Asp Ile Val Phe Leu Pro Pro Ser Phe
35 40 45

Pro Ile Val Ala Met Glu Asn Pro Cys Leu Thr Phe Ile Ile Ser Ser
50 55 60

Ile Leu Glu Ser Asp Glu Phe Leu Val Ile Asp Val Ile His Glu Val
65 70 75 80

Ala His Ser Trp Phe Gly Asn Ala Val Thr Asn Ala Thr Trp Glu Glu
85 90 95

Met Trp Leu Ser Glu Gly Leu Ala Thr Tyr Ala Gln Arg Arg Ile Thr
100 105 110

Thr Glu Thr Tyr Gly Ala Ala Phe Thr Cys Leu Glu Thr Ala Phe Arg
115 120 125

Leu Asp Ala Leu His Arg Gln Met Lys Leu Leu Gly Glu Asp Ser Pro
130 135 140

Val Ser Lys Leu Gln Val Lys Leu Glu Pro Gly Val Asn Pro Ser His
145 150 155 160

Leu Met Asn Leu Phe Thr Tyr Glu Lys Gly Tyr Cys Phe Val Tyr Tyr
165 170 175

Leu Ser Gln Leu Cys Gly Asp Pro Gln Arg Phe Asp Asp Phe Leu Arg
180 185 190

Ala Tyr Val Glu Lys Tyr Lys Phe Thr Ser Val Val Ala Gln Asp Leu
195 200 205

Leu Asp Ser Phe Leu Ser Phe Phe Pro Glu Leu Lys Glu Gln Ser Val
210 215 220

Asp Cys Arg Ala Gly Leu Glu Phe Glu Arg Trp Leu Asn Ala Thr Gly
225 230 235 240

Pro Pro Leu Ala Glu Pro Asp Leu Ser Gln Gly Ser Ser Leu Thr Arg
245 250 255

Pro Val Glu Ala Leu Phe Gln Leu Trp Thr Ala Glu Pro Leu Asp Gln
260 265 270

Ala Ala Ala Ser Ala Ser Ala Ile Asp Ile Ser Lys Trp Arg Thr Phe
275 280 285

Gln Thr Ala Leu Phe Leu Asp Arg Leu Leu Asp Gly Ser Pro Leu Pro
290 295 300

Gln Glu Val Val Met Ser Leu Ser Lys Cys Tyr Ser Ser Leu Leu Asp
305 310 315 320

Ser Met Asn Ala Glu Ile Arg Ile Arg Trp Leu Gln Ile Val Val Arg
325 330 335

Asn Asp Tyr Tyr Pro Asp Leu His Arg Val Arg Arg Phe Leu Glu Ser
340 345 350

Gln Met Ser Arg Met Tyr Thr Ile Pro Leu Tyr Glu Asp Leu Cys Thr
355 360 365

Gly Ala Leu Lys Ser Phe Ala Leu Glu Val Phe Tyr Gln Thr Gln Gly
370 375 380

Arg Leu His Pro Asn Leu Arg Arg Ala Ile Gln Gln Ile Leu Ser Gln
385 390 395 400

Gly Leu Gly Ser Ser Thr Glu Pro Ala Ser Glu Pro Ser Thr Glu Leu
405 410 415

Gly Lys Ala Glu Ala Asp Thr Asp Ser Asp Ala Gln Ala Leu Leu Leu
420 425 430

Gly Asp Glu Ala Pro Ser Ser Ala Ile Ser Leu Arg Asp Val Asn Val
435 440 445

Ser Ala
450

<210> 346
<211> 366
<212> PRT
<213> Homo sapien

<400> 346

Gly Ser Glu Gln Gln Ser Gln Trp Cys Val Ser Pro Gln Ser Ser Pro
1 5 10 15

Arg Pro Cys Arg Cys Thr Pro Arg Ala Ser Val His Ile Trp Thr Cys
20 25 30

Glu Gly Gln Trp Arg Leu Ala Leu Ala Ala Pro Arg Ser Leu Thr Thr
35 40 45

Ala Pro Pro Tyr Ser Thr Gly His Trp Trp Phe Arg Thr Pro Ala Gln
50 55 60

Val Gly Val His Leu Ala Gly Val Asn Pro Ser His Leu Met Asn Leu
65 70 75 80

Phe Thr Tyr Glu Lys Gly Tyr Cys Phe Val Tyr Tyr Leu Ser Gln Leu
85 90 95

Cys Gly Asp Pro Gln Arg Phe Asp Asp Phe Leu Arg Ala Tyr Val Glu
100 105 110

Lys Tyr Lys Phe Thr Ser Val Val Ala Gln Asp Leu Leu Asp Ser Phe
115 120 125

Leu Ser Phe Phe Pro Glu Leu Lys Glu Gln Ser Val Asp Cys Arg Ala
130 135 140

Gly Leu Glu Phe Glu Arg Trp Leu Asn Ala Thr Gly Pro Pro Leu Ala
145 150 155 160

Glu Pro Asp Leu Ser Gln Gly Ser Ser Leu Thr Arg Pro Val Glu Ala
165 170 175

Leu Phe Gln Leu Trp Thr Ala Glu Pro Leu Asp Gln Ala Ala Ala Ser
180 185 190

Ala Ser Ala Ile Asp Ile Ser Lys Trp Arg Thr Phe Gln Thr Ala Leu

195 200 205

Phe Leu Asp Arg Leu Leu Asp Gly Ser Pro Leu Pro Gln Glu Val Val
210 215 220

Met Ser Leu Ser Lys Cys Tyr Ser Ser Leu Leu Asp Ser Met Asn Ala
225 230 235 240

Glu Ile Arg Ile Arg Trp Leu Gln Ile Val Val Arg Asn Asp Tyr Tyr
245 250 255

Pro Asp Leu His Arg Val Arg Arg Phe Leu Glu Ser Gln Met Ser Arg
260 265 270

Met Tyr Thr Ile Pro Leu Tyr Glu Asp Leu Cys Thr Gly Ala Leu Lys
275 280 285

Ser Phe Ala Leu Glu Val Phe Tyr Gln Thr Gln Gly Arg Leu His Pro
290 295 300

Asn Leu Arg Arg Ala Ile Gln Gln Ile Leu Ser Gln Gly Leu Gly Ser
305 310 315 320

Ser Thr Glu Pro Ala Ser Glu Pro Ser Thr Glu Leu Gly Lys Ala Glu
325 330 335

Ala Asp Thr Asp Ser Asp Ala Gln Ala Leu Leu Leu Gly Asp Glu Ala
340 345 350

Pro Ser Ser Ala Ile Ser Leu Arg Asp Val Asn Val Ser Ala
355 360 365

<210> 347
<211> 756
<212> PRT
<213> Homo sapien

<400> 347

Val Ala Gly Val Pro Pro Ala Ala Ala Glu Thr Pro Cys Ala Phe Ala
1 5 10 15

Phe Ser Ala Pro Gly Pro Gly Pro Ala Pro Pro Pro Pro Leu Pro Ala
20 25 30

Phe Pro Glu Ala Pro Gly Ser Glu Pro Ala Cys Cys Pro Leu Ala Phe
35 40 45

Arg Val Asp Pro Phe Thr Asp Tyr Gly Ser Ser Leu Thr Val Thr Leu
50 55 60

Pro Pro Glu Leu Gln Ala His Gln Pro Phe Gln Val Ile Leu Arg Tyr
65 70 75 80

Thr Ser Thr Asp Ala Pro Ala Ile Trp Trp Leu Asp Pro Glu Leu Thr
85 90 95

Tyr Gly Cys Ala Lys Pro Phe Val Phe Thr Gln Gly His Ser Val Cys
100 105 110

Asn Arg Ser Phe Phe Pro Cys Phe Asp Thr Pro Ala Val Lys Cys Thr
115 120 125

Tyr Ser Ala Val Val Lys Ala Pro Ser Gly Val Gln Val Leu Met Ser
130 135 140

Ala Thr Arg Ser Ala Tyr Met Glu Glu Glu Gly Val Phe His Phe His
145 150 155 160

Met Glu His Pro Val Pro Ala Tyr Leu Val Ala Leu Val Ala Gly Asp
165 170 175

Leu Lys Pro Ala Asp Ile Gly Pro Arg Ser Arg Val Trp Ala Glu Pro
180 185 190

Cys Leu Leu Pro Thr Ala Thr Ser Lys Leu Ser Gly Ala Val Glu Gln
195 200 205

Trp Leu Ser Ala Ala Glu Arg Leu Tyr Gly Pro Tyr Met Trp Gly Arg
210 215 220

Tyr Asp Ile Val Phe Leu Pro Pro Ser Phe Pro Ile Val Ala Met Glu
225 230 235 240

Asn Pro Cys Leu Thr Phe Ile Ile Ser Ser Ile Leu Glu Ser Asp Glu
245 250 255

Phe Leu Val Ile Asp Val Ile His Glu Val Ala His Ser Trp Phe Gly
260 265 270

Asn Ala Val Thr Asn Ala Thr Trp Glu Glu Met Trp Leu Ser Glu Gly
275 280 285

Leu Ala Thr Tyr Ala Gln Arg Arg Ile Thr Thr Glu Thr Tyr Gly Ala
290 295 300

Ala Phe Thr Cys Leu Glu Thr Ala Phe Arg Leu Asp Ala Leu His Arg
305 310 315 320

Gln Met Lys Leu Leu Gly Glu Asp Ser Pro Val Ser Lys Leu Gln Val
325 330 335

Lys Leu Glu Pro Gly Val Asn Pro Ser His Leu Met Asn Leu Phe Thr
340 345 350

Tyr Glu Lys Gly Tyr Cys Phe Val Tyr Tyr Leu Ser Gln Leu Cys Gly
355 360 365

Asp Pro Gln Arg Phe Asp Asp Phe Leu Arg Val Ser Ser Pro Leu Pro
370 375 380

Gly Thr Ala Leu Leu Pro Ser Ala Pro Ser Pro Ser Pro Ala His Arg
385 390 395 400

Ala Ala Cys Ser Cys Gly Ser Trp Gly Gly Thr Gly Arg Gly Leu Gly
405 410 415

Ala Trp Leu Gly Pro Ser Leu Pro Phe Phe Val Gly Ser Ala Trp Val
420 425 430

Ala Thr Ser Pro Ser Ala Thr Leu Phe Ala Pro Leu Ala Gly Pro Ala
435 440 445

Cys Gln Val Leu Ala Pro Gln Cys Pro Leu Ala Ala Pro Val Pro Ser
450 455 460

Thr Tyr Leu Gly Ala Arg Pro Ala Val Pro Cys Arg Pro Leu Val Gly
465 470 475 480

Leu Pro Val Pro His Pro Ser Arg Pro Ala Glu Ala Pro Pro Pro Ala
485 490 495

Thr Gln Ala Tyr Val Glu Lys Tyr Lys Phe Thr Ser Val Val Ala Gln
500 505 510

Asp Leu Leu Asp Ser Phe Leu Ser Phe Phe Pro Glu Leu Lys Glu Gln
515 520 525

Ser Val Asp Cys Arg Ala Gly Leu Glu Phe Glu Arg Trp Leu Asn Ala

530 535 540

Thr Gly Pro Pro Leu Ala Glu Pro Asp Leu Ser Gln Gly Ser Ser Leu
545 550 555 560

Thr Arg Pro Val Glu Ala Leu Phe Gln Leu Trp Thr Ala Glu Pro Leu
565 570 575

Asp Gln Ala Ala Ala Ser Ala Ser Ala Ile Asp Ile Ser Lys Trp Arg
580 585 590

Thr Phe Gln Thr Ala Leu Phe Leu Asp Arg Leu Leu Asp Gly Ser Pro
595 600 605

Leu Pro Gln Glu Val Val Met Ser Leu Ser Lys Cys Tyr Ser Ser Leu
610 615 620

Leu Asp Ser Met Asn Ala Glu Ile Arg Ile Arg Trp Leu Gln Ile Val
625 630 635 640

Val Arg Asn Asp Tyr Tyr Pro Asp Leu His Arg Val Arg Arg Phe Leu
645 650 655

Glu Ser Gln Met Ser Arg Met Tyr Thr Ile Pro Leu Tyr Glu Asp Leu
660 665 670

Cys Thr Gly Ala Leu Lys Ser Phe Ala Leu Glu Val Phe Tyr Gln Thr
675 680 685

Gln Gly Arg Leu His Pro Asn Leu Arg Arg Ala Ile Gln Gln Ile Leu
690 695 700

Ser Gln Gly Leu Gly Ser Ser Thr Glu Pro Ala Ser Glu Pro Ser Thr
705 710 715 720

Glu Leu Gly Lys Ala Glu Ala Asp Thr Asp Ser Asp Ala Gln Ala Leu
725 730 735

Leu Leu Gly Asp Glu Ala Pro Ser Ser Ala Ile Ser Leu Arg Asp Val
740 745 750

Asn Val Ser Ala
755

<210> 348
<211> 38

<212> PRT
<213> Homo sapien

<400> 348

Met Ser Lys Asn Phe Ile Phe Thr Asn Leu Ile Asp Gln Lys Asp Thr
1 5 10 15

Leu Leu Ala Phe Phe Thr Ile Cys Lys Ala Lys Asn His Gln Asn Ser
20 25 30

Pro Ser Pro His Ile Tyr
35

<210> 349
<211> 231
<212> PRT
<213> Homo sapien

<400> 349

Met Leu Glu Arg Arg Ser Val Met Asp Arg Arg Pro Gly Arg Glu Phe
1 5 10 15

Asp Gly Ile Leu Gly Leu Gly Tyr Pro Ser Leu Ala Val Gly Gly Val
20 25 30

Thr Pro Val Phe Asp Asn Met Met Ala Gln Asn Leu Val Asp Leu Pro
35 40 45

Met Phe Ser Val Tyr Met Ser Ser Asn Pro Glu Gly Gly Ala Gly Ser
50 55 60

Glu Leu Ile Phe Gly Gly Tyr Asp His Ser His Phe Ser Gly Ser Leu
65 70 75 80

Asn Trp Val Pro Val Thr Lys Gln Ala Tyr Trp Gln Ile Ala Leu Asp
85 90 95

Asn Ile Gln Val Gly Gly Thr Val Met Phe Cys Ser Glu Gly Cys Gln
100 105 110

Ala Ile Val Asp Thr Gly Thr Ser Leu Ile Thr Gly Pro Ser Asp Lys
115 120 125

Ile Lys Gln Leu Gln Asn Ala Ile Gly Ala Ala Pro Val Asp Gly Glu
130 135 140

Tyr Ala Val Glu Cys Ala Asn Leu Asn Val Met Pro Asp Val Thr Phe

145 150 155 160

Thr Ile Asn Gly Val Pro Tyr Thr Leu Ser Pro Thr Ala Tyr Thr Leu
165 170 175

Leu Asp Phe Val Asp Gly Met Gln Phe Cys Ser Ser Gly Phe Gln Gly
180 185 190

Leu Asp Ile His Pro Pro Ala Gly Pro Leu Trp Ile Leu Gly Asp Val
195 200 205

Phe Ile Arg Gln Phe Tyr Ser Val Phe Asp Arg Gly Asn Asn Arg Val
210 215 220

Gly Leu Ala Pro Ala Val Pro
225 230

<210> 350
<211> 47
<212> PRT
<213> Homo sapien

<400> 350

Met Ser Val Asn Met Tyr Tyr Arg Arg Ser Tyr Ser Leu Ser Phe Cys
1 5 10 15

Phe Arg Phe Tyr Val Leu Leu Pro Phe Ser Asn Lys Ser Met Lys Gly
20 25 30

Lys Arg Ile Ser Thr Arg Asn Ile His Phe Phe Pro Ser Gln Ile
35 40 45

<210> 351
<211> 361
<212> PRT
<213> Homo sapien

<400> 351

Thr Gly Ile Ser Leu Ala Ser Gln Leu Lys Val Pro Pro Tyr Ala Ser
1 5 10 15

Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys Glu Tyr Tyr Glu Pro Gln
20 25 30

His Arg Ile Cys Cys Ser Arg Cys Pro Pro Gly Thr Tyr Val Ser Ala
35 40 45

Lys Cys Ser Arg Ile Arg Asp Thr Val Cys Ala Thr Cys Ala Glu Asn
50 55 60

Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr Ile Cys Gln Leu Cys Arg
65 70 75 80

Pro Cys Asp Pro Val Met Gly Leu Glu Glu Ile Ala Pro Cys Thr Ser
85 90 95

Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro Gly Met Phe Cys Ala Ala
100 105 110

Trp Ala Leu Glu Cys Thr His Cys Glu Arg Leu Ser Asp Cys Pro Pro
115 120 125

Gly Thr Glu Ala Glu Leu Lys Asp Glu Val Gly Lys Gly Asn Asn His
130 135 140

Cys Val Pro Cys Lys Ala Gly His Phe Gln Asn Thr Ser Ser Pro Ser
145 150 155 160

Ala Leu Cys Gln Pro His Thr Arg Cys Glu Asn Gln Gly Leu Val Glu
165 170 175

Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr Thr Cys Lys Asn Pro Leu
180 185 190

Glu Pro Leu Pro Pro Glu Met Ser Gly Ser Leu Leu Lys Arg Arg Pro
195 200 205

Gln Gly Glu Gly Pro Asn Pro Val Ala Gly Ser Trp Glu Pro Pro Lys
210 215 220

Ala His Pro Tyr Phe Pro Asp Leu Val Gln Pro Leu Leu Pro Ile Ser
225 230 235 240

Gly Asp Val Ser Pro Val Ser Thr Gly Leu Pro Ala Ala Pro Val Leu
245 250 255

Glu Ala Gly Val Pro Gln Gln Gln Ser Pro Leu Asp Leu Thr Arg Glu
260 265 270

Pro Gln Leu Glu Pro Gly Glu Gln Ser Gln Val Ala His Gly Thr Asn
275 280 285

Gly Ile His Val Thr Gly Gly Ser Met Thr Ile Thr Gly Asn Ile Tyr

290 295 300

Ile Tyr Asn Gly Pro Val Leu Gly Gly Pro Pro Gly Pro Gly Asp Leu
305 310 315 320

Pro Ala Thr Pro Glu Pro Pro Tyr Pro Ile Pro Glu Glu Gly Asp Pro
325 330 335

Gly Pro Pro Gly Leu Ser Thr Pro His Gln Glu Asp Gly Lys Ala Trp
340 345 350

His Leu Ala Glu Thr Glu His Cys Gly
355 360

<210> 352
<211> 399
<212> PRT
<213> Homo sapien

<400> 352

Met Leu Leu Pro Trp Ala Thr Ser Ala Pro Gly Leu Ala Trp Gly Pro
1 5 10 15

Leu Val Leu Gly Leu Phe Gly Leu Leu Ala Ala Ser Gln Pro Gln Ala
20 25 30

Val Pro Pro Tyr Ala Ser Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys
35 40 45

Glu Tyr Tyr Glu Pro Gln His Arg Ile Cys Cys Ser Arg Cys Pro Pro
50 55 60

Gly Thr Tyr Val Ser Ala Lys Cys Ser Arg Ile Arg Asp Thr Val Cys
65 70 75 80

Ala Thr Cys Ala Glu Asn Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr
85 90 95

Ile Cys Gln Leu Cys Arg Pro Cys Asp Pro Val Met Gly Leu Glu Glu
100 105 110

Ile Ala Pro Cys Thr Ser Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro
115 120 125

Gly Met Phe Cys Ala Ala Trp Ala Leu Glu Cys Thr His Cys Glu Leu
130 135 140

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Leu Ser Asp Cys Pro Pro Gly Thr Glu Ala Glu Leu Lys Asp Glu Val
145                 150                 155                 160

Gly Lys Gly Asn Asn His Cys Val Pro Cys Lys Ala Gly His Phe Gln
                165                 170                 175

Asn Thr Ser Ser Pro Ser Ala Arg Cys Gln Pro His Thr Arg Cys Glu
            180                 185                 190

Asn Gln Gly Leu Val Glu Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr
        195                 200                 205

Thr Cys Lys Asn Pro Leu Glu Pro Leu Pro Pro Glu Met Ser Gly Ser
    210                 215                 220

Leu Leu Lys Arg Arg Pro Gln Gly Glu Gly Pro Asn Pro Val Ala Gly
225                 230                 235                 240

Ser Trp Glu Pro Pro Lys Ala His Pro Tyr Phe Pro Asp Leu Val Gln
                245                 250                 255

Pro Leu Leu Pro Ile Ser Gly Asp Val Ser Pro Val Ser Thr Gly Leu
            260                 265                 270

Pro Ala Ala Pro Val Leu Glu Ala Gly Val Pro Gln Gln Gln Ser Pro
        275                 280                 285

Leu Asp Leu Thr Arg Glu Pro Gln Leu Glu Pro Gly Glu Gln Ser Gln
    290                 295                 300

Val Ala His Gly Thr Asn Gly Ile His Val Thr Gly Gly Ser Met Thr
305                 310                 315                 320

Ile Thr Gly Asn Ile Tyr Ile Tyr Asn Gly Pro Val Leu Gly Gly Pro
                325                 330                 335

Pro Gly Pro Gly Asp Leu Pro Ala Thr Pro Glu Pro Pro Tyr Pro Ile
            340                 345                 350

Pro Glu Glu Gly Asp Pro Gly Pro Pro Gly Leu Ser Thr Pro His Gln
        355                 360                 365

Glu Asp Gly Lys Ala Trp His Leu Ala Glu Thr Glu His Cys Gly Ala
    370                 375                 380
```

Thr Pro Ser Asn Arg Gly Pro Arg Asn Gln Phe Ile Thr His Asp
385 390 395

<210> 353
<211> 435
<212> PRT
<213> Homo sapien

<400> 353

Met Leu Leu Pro Trp Ala Thr Ser Ala Pro Gly Leu Ala Trp Gly Pro
1 5 10 15

Leu Val Leu Gly Leu Phe Gly Leu Leu Ala Ala Ser Gln Pro Gln Ala
20 25 30

Val Pro Pro Tyr Ala Ser Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys
35 40 45

Glu Tyr Tyr Glu Pro Gln His Arg Ile Cys Cys Ser Arg Cys Pro Pro
50 55 60

Gly Thr Tyr Val Ser Ala Lys Cys Ser Arg Ile Arg Asp Thr Val Cys
65 70 75 80

Ala Thr Cys Ala Glu Asn Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr
85 90 95

Ile Cys Gln Leu Cys Arg Pro Cys Asp Pro Val Met Gly Leu Glu Glu
100 105 110

Ile Ala Pro Cys Thr Ser Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro
115 120 125

Gly Met Phe Cys Ala Ala Trp Ala Leu Glu Cys Thr His Cys Glu Leu
130 135 140

Leu Ser Asp Cys Pro Pro Gly Thr Glu Ala Glu Leu Lys Asp Glu Val
145 150 155 160

Gly Lys Gly Asn Asn His Cys Val Pro Cys Lys Ala Gly His Phe Gln
165 170 175

Asn Thr Ser Ser Pro Ser Ala Arg Cys Gln Pro His Thr Arg Cys Glu
180 185 190

Asn Gln Gly Leu Val Glu Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr
195 200 205

```
Thr Cys Lys Asn Pro Leu Glu Pro Leu Pro Pro Glu Met Ser Gly Thr
    210                 215                 220

Met Leu Met Leu Ala Val Leu Leu Pro Leu Ala Phe Phe Leu Leu Leu
225                 230                 235                 240

Ala Thr Val Phe Ser Cys Ile Trp Lys Ser His Pro Ser Leu Cys Arg
                245                 250                 255

Lys Leu Gly Ser Leu Leu Lys Arg Arg Pro Gln Gly Glu Gly Pro Asn
            260                 265                 270

Pro Val Ala Gly Ser Trp Glu Pro Pro Lys Ala His Pro Tyr Phe Pro
        275                 280                 285

Asp Leu Val Gln Pro Leu Leu Pro Ile Ser Gly Asp Val Ser Pro Val
    290                 295                 300

Ser Thr Gly Leu Pro Ala Ala Pro Val Leu Glu Ala Gly Val Pro Gln
305                 310                 315                 320

Gln Gln Ser Pro Leu Asp Leu Thr Arg Glu Pro Gln Leu Glu Pro Gly
                325                 330                 335

Glu Gln Ser Gln Val Ala His Gly Thr Asn Gly Ile His Val Thr Gly
            340                 345                 350

Gly Ser Met Thr Ile Thr Gly Asn Ile Tyr Ile Tyr Asn Gly Pro Val
        355                 360                 365

Leu Gly Gly Pro Pro Gly Pro Gly Asp Leu Pro Ala Thr Pro Glu Pro
    370                 375                 380

Pro Tyr Pro Ile Pro Glu Glu Gly Asp Pro Gly Pro Pro Gly Leu Ser
385                 390                 395                 400

Thr Pro His Gln Glu Asp Gly Lys Ala Trp His Leu Ala Glu Thr Glu
                405                 410                 415

His Cys Gly Ala Thr Pro Ser Asn Arg Gly Pro Arg Asn Gln Phe Ile
            420                 425                 430

Thr His Asp
        435
```

<210> 354
<211> 450
<212> PRT
<213> Homo sapien

<400> 354

Met Leu Leu Pro Trp Ala Thr Ser Ala Pro Gly Leu Ala Trp Gly Pro
1 5 10 15

Leu Val Leu Gly Leu Phe Gly Leu Leu Ala Ala Ser Gln Pro Gln Ala
20 25 30

Val Pro Pro Tyr Ala Ser Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys
35 40 45

Glu Tyr Tyr Glu Pro Gln His Arg Ile Cys Cys Ser Arg Cys Pro Pro
50 55 60

Gly Thr Tyr Val Ser Ala Lys Cys Ser Arg Ile Arg Asp Thr Val Cys
65 70 75 80

Ala Thr Cys Ala Glu Asn Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr
85 90 95

Ile Cys Gln Leu Cys Arg Pro Cys Asp Pro Val Met Gly Leu Glu Glu
100 105 110

Ile Ala Pro Cys Thr Ser Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro
115 120 125

Gly Met Phe Cys Ala Ala Trp Ala Leu Glu Cys Thr His Cys Glu Leu
130 135 140

Leu Ser Asp Cys Pro Pro Gly Thr Glu Ala Glu Leu Lys Asp Glu Val
145 150 155 160

Gly Lys Gly Asn Asn His Cys Val Pro Cys Lys Ala Gly His Phe Gln
165 170 175

Asn Thr Ser Ser Pro Ser Ala Arg Cys Gln Pro His Thr Arg Cys Glu
180 185 190

Asn Gln Gly Leu Val Glu Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr
195 200 205

Thr Cys Lys Asn Pro Leu Glu Pro Leu Pro Pro Glu Met Ser Gly Thr

210 215 220

Met Leu Met Leu Ala Val Leu Leu Pro Leu Ala Phe Phe Leu Leu Leu
225 230 235 240

Ala Thr Val Phe Ser Cys Ile Trp Lys Ser His Pro Ser Leu Cys Arg
245 250 255

Lys Leu Gly Ser Leu Leu Lys Arg Arg Pro Gln Gly Glu Gly Pro Asn
260 265 270

Pro Val Ala Gly Ser Trp Glu Pro Pro Lys Ala His Pro Tyr Phe Pro
275 280 285

Asp Leu Val Gln Pro Leu Leu Pro Ile Ser Gly Asp Val Ser Pro Val
290 295 300

Ser Thr Gly Leu Pro Ala Ala Pro Val Leu Glu Ala Gly Val Pro Gln
305 310 315 320

Gln Gln Ser Pro Leu Asp Leu Thr Arg Glu Pro Gln Leu Glu Pro Gly
325 330 335

Glu Gln Ser Gln Val Ala His Gly Thr Asn Gly Ile His Val Thr Gly
340 345 350

Gly Ser Met Thr Ile Thr Gly Asn Ile Tyr Ile Tyr Asn Gly Pro Val
355 360 365

Leu Gly Gly Pro Pro Gly Pro Gly Asp Leu Pro Ala Thr Pro Glu Pro
370 375 380

Pro Tyr Pro Ile Pro Glu Glu Gly Asp Pro Gly Pro Pro Gly Leu Ser
385 390 395 400

Thr Pro His Gln Glu Asp Gly Lys Ala Trp His Leu Ala Glu Thr Glu
405 410 415

His Cys Gly Ala Thr Pro Ser Lys Gly Phe Val Val Leu Ile Pro Lys
420 425 430

Leu Gln Arg Pro Phe Gly Val Pro His Phe Thr Trp Thr Glu Val Asp
435 440 445

Pro Ala
450

<210> 355
<211> 635
<212> PRT
<213> Homo sapien

<400> 355

Met Leu Leu Pro Trp Ala Thr Ser Ala Pro Gly Leu Ala Trp Gly Pro
1 5 10 15

Leu Val Leu Gly Leu Phe Gly Leu Leu Ala Ala Ser Gln Pro Gln Ala
20 25 30

Val Pro Pro Tyr Ala Ser Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys
35 40 45

Glu Tyr Tyr Glu Pro Gln His Arg Ile Cys Cys Ser Arg Cys Pro Pro
50 55 60

Gly Thr Tyr Val Ser Ala Lys Cys Ser Arg Ile Arg Asp Thr Val Cys
65 70 75 80

Ala Thr Cys Ala Glu Asn Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr
85 90 95

Ile Cys Gln Leu Cys Arg Pro Cys Asp Pro Val Met Gly Leu Glu Glu
100 105 110

Ile Ala Pro Cys Thr Ser Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro
115 120 125

Gly Met Phe Cys Ala Ala Trp Ala Leu Glu Cys Thr His Cys Glu Leu
130 135 140

Leu Ser Asp Cys Pro Pro Gly Thr Glu Ala Glu Leu Lys Asp Glu Val
145 150 155 160

Gly Lys Gly Asn Asn His Cys Val Pro Cys Lys Ala Gly His Phe Gln
165 170 175

Asn Thr Ser Ser Pro Ser Ala Arg Cys Gln Pro His Thr Arg Cys Glu
180 185 190

Asn Gln Gly Leu Val Glu Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr
195 200 205

Thr Cys Lys Asn Pro Leu Glu Pro Leu Pro Pro Glu Met Ser Glu Pro
210 215 220

Ala Leu Ser Lys Gly Val Glu Asn Leu Gln Ala Leu Leu Tyr Gln Ala
225 230 235 240

Ala Thr Gly Ser Ser Glu Ala Ser Phe Pro Thr Leu Ser Pro Leu Tyr
245 250 255

Thr Pro Pro Gln Val Gln Val Gln Gln Gly Asn Pro Glu Leu Leu Tyr
260 265 270

Ser Ser Pro Ser Val Gln Trp Leu Arg Pro Gln Lys Cys Gly Ser Ser
275 280 285

Leu Cys Leu Phe Thr Thr Pro Ser Pro Thr Leu Pro Tyr Cys Leu Pro
290 295 300

Ile Pro Leu Pro Asp Leu Glu Asn Gln Leu Pro Lys Leu Pro Ser Cys
305 310 315 320

Thr His Lys Pro Ala Gln Ser Trp Ser Leu Ser Arg Arg Ala Pro Thr
325 330 335

Pro Pro Pro Asn Met Pro Ile His Asp Thr Val Ser Pro Gly Cys Gln
340 345 350

Glu Val Leu Lys Ser Asn Leu Val Pro Leu Leu Tyr Asn Pro Arg Glu
355 360 365

Val Ser Leu Ile Leu Pro Leu Gly Ala Ala Leu Cys Leu Glu Gly Lys
370 375 380

Lys Leu Leu Pro Phe Leu Cys Leu Gly Cys Pro Gly Ile Trp Lys Ala
385 390 395 400

Leu Pro Ser Pro Pro Pro Ser Ala Leu Leu Gly Ala Val Ile Thr Leu
405 410 415

Leu Ser Ala Val Leu Ala Gly Thr Met Leu Met Leu Ala Val Leu Leu
420 425 430

Pro Leu Ala Phe Phe Leu Leu Leu Ala Thr Val Phe Ser Cys Ile Trp
435 440 445

Lys Ser His Pro Ser Leu Cys Arg Lys Leu Gly Ser Leu Leu Lys Arg

450 455 460

Arg Pro Gln Gly Glu Gly Pro Asn Pro Val Ala Gly Ser Trp Glu Pro
465 470 475 480

Pro Lys Ala His Pro Tyr Phe Pro Asp Leu Val Gln Pro Leu Leu Pro
485 490 495

Ile Ser Gly Asp Val Ser Pro Val Ser Thr Gly Leu Pro Ala Ala Pro
500 505 510

Val Leu Glu Ala Gly Val Pro Gln Gln Gln Ser Pro Leu Asp Leu Thr
515 520 525

Arg Glu Pro Gln Leu Glu Pro Gly Glu Gln Ser Gln Val Ala His Gly
530 535 540

Thr Asn Gly Ile His Val Thr Gly Gly Ser Met Thr Ile Thr Gly Asn
545 550 555 560

Ile Tyr Ile Tyr Asn Gly Pro Val Leu Gly Gly Pro Pro Gly Pro Gly
565 570 575

Asp Leu Pro Ala Thr Pro Glu Pro Pro Tyr Pro Ile Pro Glu Glu Gly
580 585 590

Asp Pro Gly Pro Pro Gly Leu Ser Thr Pro His Gln Glu Asp Gly Lys
595 600 605

Ala Trp His Leu Ala Glu Thr Glu His Cys Gly Ala Thr Pro Ser Asn
610 615 620

Arg Gly Pro Arg Asn Gln Phe Ile Thr His Asp
625 630 635

<210> 356
<211> 194
<212> PRT
<213> Homo sapien

<400> 356

Lys Lys Arg Glu Gly Gly Arg Glu Lys Lys Gly Ser Gly Ala Leu Ile
1 5 10 15

Ile Val Trp Val Ser Ile Ser Phe Leu Gln Gly Glu Gly Pro Asn Pro
20 25 30

Val Ala Gly Ser Trp Glu Pro Pro Lys Ala His Pro Tyr Phe Pro Asp
35 40 45

Leu Val Gln Pro Leu Leu Pro Ile Ser Gly Asp Val Ser Pro Val Ser
50 55 60

Thr Gly Leu Pro Ala Ala Pro Val Leu Glu Ala Gly Val Pro Gln Gln
65 70 75 80

Gln Ser Pro Leu Asp Leu Thr Arg Glu Pro Gln Leu Glu Pro Gly Glu
85 90 95

Gln Ser Gln Val Ala His Gly Thr Asn Gly Ile His Val Thr Gly Gly
100 105 110

Ser Met Thr Ile Thr Gly Asn Ile Tyr Ile Tyr Asn Gly Pro Val Leu
115 120 125

Gly Gly Pro Pro Gly Pro Gly Asp Leu Pro Ala Thr Pro Glu Pro Pro
130 135 140

Tyr Pro Ile Pro Glu Glu Gly Asp Pro Gly Pro Pro Gly Leu Ser Thr
145 150 155 160

Pro His Gln Glu Asp Gly Lys Ala Trp His Leu Ala Glu Thr Glu His
165 170 175

Cys Gly Ala Thr Pro Ser Asn Arg Gly Pro Arg Asn Gln Phe Ile Thr
180 185 190

His Asp

<210> 357
<211> 305
<212> PRT
<213> Homo sapien

<400> 357

Met Leu Leu Pro Trp Ala Thr Ser Ala Pro Gly Leu Ala Trp Gly Pro
1 5 10 15

Leu Val Leu Gly Leu Phe Gly Leu Leu Ala Ala Ser Gln Pro Gln Ala
20 25 30

Val Pro Pro Tyr Ala Ser Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys

35 40 45

Glu Tyr Tyr Glu Pro Gln His Arg Ile Cys Cys Ser Arg Cys Pro Pro
50 55 60

Gly Thr Tyr Val Ser Ala Lys Cys Ser Arg Ile Arg Asp Thr Val Cys
65 70 75 80

Ala Thr Cys Ala Glu Asn Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr
85 90 95

Ile Cys Gln Leu Cys Arg Pro Cys Asp Pro Val Met Gly Leu Glu Glu
100 105 110

Ile Ala Pro Cys Thr Ser Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro
115 120 125

Gly Met Phe Cys Ala Ala Trp Ala Leu Glu Cys Thr His Cys Glu Leu
130 135 140

Leu Ser Asp Cys Pro Pro Gly Thr Glu Ala Glu Leu Lys Asp Glu Val
145 150 155 160

Gly Lys Gly Asn Asn His Cys Val Pro Cys Lys Ala Gly His Phe Gln
165 170 175

Asn Thr Ser Ser Pro Ser Ala Arg Cys Gln Pro His Thr Arg Cys Glu
180 185 190

Asn Gln Gly Leu Val Glu Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr
195 200 205

Thr Cys Lys Asn Pro Leu Glu Pro Leu Pro Pro Glu Met Ser Gly Thr
210 215 220

Met Leu Met Leu Ala Val Leu Leu Pro Leu Ala Phe Phe Leu Leu Leu
225 230 235 240

Ala Thr Val Phe Ser Cys Ile Trp Lys Ser His Pro Ser Leu Cys Arg
245 250 255

Lys Leu Gly Ser Leu Leu Lys Arg Arg Pro Gln Val Met Ala Gly Ala
260 265 270

Glu Lys Ala Ala Arg Arg Gly Arg Gly Asp Glu Gly Thr Arg Trp Ser
275 280 285

```
Arg Gln Glu Glu Ser Met Gln Ala Asp Ser Thr Leu Ile His Ser Phe
    290                 295                 300

Asn
305
```

<210> 358
<211> 1127
<212> PRT
<213> Homo sapien

<400> 358

```
Met Trp Ser Leu Thr Ala Ser Glu Gly Glu Ser Thr Thr Ala His Phe
1               5                  10                  15

Phe Leu Gly Ala Gly Asp Glu Gly Leu Gly Thr Arg Gly Ile Gly Met
            20                  25                  30

Arg Pro Glu Glu Ser Asp Ser Glu Leu Leu Glu Asp Glu Glu Asp Glu
        35                  40                  45

Val Pro Pro Glu Pro Gln Ile Ile Val Gly Ile Cys Ala Met Thr Lys
    50                  55                  60

Lys Ser Lys Ser Lys Pro Met Thr Gln Ile Leu Glu Arg Leu Cys Arg
65                  70                  75                  80

Phe Asp Tyr Leu Thr Val Val Ile Leu Gly Glu Asp Val Ile Leu Asn
                85                  90                  95

Glu Pro Val Glu Asn Trp Pro Ser Cys His Cys Leu Ile Ser Phe His
            100                 105                 110

Ser Lys Gly Phe Pro Leu Asp Lys Ala Val Ala Tyr Ser Lys Leu Arg
        115                 120                 125

Asn Pro Phe Leu Ile Asn Asp Leu Ala Met Gln Tyr Tyr Ile Gln Asp
    130                 135                 140

Arg Arg Glu Val Tyr Arg Ile Leu Gln Glu Glu Gly Ile Asp Leu Pro
145                 150                 155                 160

Arg Tyr Ala Val Leu Asn Arg Asp Pro Ala Arg Pro Glu Glu Cys Asn
                165                 170                 175
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Leu Ile Glu Gly Glu Asp Gln Val Glu Val Asn Gly Ala Val Phe Pro
180 185 190

Lys Pro Phe Val Glu Lys Pro Val Ser Ala Glu Asp His Asn Val Tyr
195 200 205

Ile Tyr Tyr Pro Ser Ser Ala Gly Gly Gly Ser Gln Arg Leu Phe Arg
210 215 220

Lys Ile Gly Ser Arg Ser Ser Val Tyr Ser Pro Glu Ser Ser Val Arg
225 230 235 240

Lys Thr Gly Ser Tyr Ile Tyr Glu Glu Phe Met Pro Thr Asp Gly Thr
245 250 255

Asp Val Lys Val Tyr Thr Val Gly Pro Asp Tyr Ala His Ala Glu Ala
260 265 270

Arg Lys Ser Pro Ala Leu Asp Gly Lys Val Glu Arg Asp Ser Glu Gly
275 280 285

Lys Glu Ile Arg Tyr Pro Val Met Leu Thr Ala Met Glu Lys Leu Val
290 295 300

Ala Arg Lys Val Cys Val Ala Phe Lys Gln Thr Val Cys Gly Phe Asp
305 310 315 320

Leu Leu Arg Ala Asn Gly His Ser Phe Val Cys Asp Val Asn Gly Phe
325 330 335

Ser Phe Val Lys Asn Ser Met Lys Tyr Tyr Asp Asp Cys Ala Lys Ile
340 345 350

Leu Gly Asn Thr Ile Met Arg Glu Leu Ala Pro Gln Phe Gln Ile Pro
355 360 365

Trp Ser Ile Pro Thr Glu Ala Glu Asp Ile Pro Ile Val Pro Thr Thr
370 375 380

Ser Gly Thr Met Met Glu Leu Arg Cys Val Ile Ala Ile Ile Arg His
385 390 395 400

Gly Asp Arg Thr Pro Lys Gln Lys Met Lys Met Glu Val Lys His Pro
405 410 415

Arg Phe Phe Ala Leu Phe Glu Lys His Gly Gly Tyr Lys Thr Gly Lys

420 425 430

Leu Lys Leu Lys Arg Pro Glu Gln Leu Gln Glu Val Leu Asp Ile Thr
435 440 445

Arg Leu Leu Leu Ala Glu Leu Glu Lys Glu Pro Gly Gly Glu Ile Glu
450 455 460

Glu Lys Thr Gly Lys Leu Glu Gln Leu Lys Ser Val Leu Glu Met Tyr
465 470 475 480

Gly His Phe Ser Gly Ile Asn Arg Lys Val Gln Leu Thr Tyr Tyr Pro
485 490 495

His Gly Val Lys Ala Ser Asn Glu Gly Gln Asp Pro Gln Arg Glu Thr
500 505 510

Leu Ala Pro Ser Leu Leu Leu Val Leu Lys Trp Gly Gly Glu Leu Thr
515 520 525

Pro Ala Gly Arg Val Gln Ala Glu Glu Leu Gly Arg Ala Phe Arg Cys
530 535 540

Met Tyr Pro Gly Gly Gln Gly Asp Tyr Ala Gly Phe Pro Gly Cys Gly
545 550 555 560

Leu Leu Arg Leu His Ser Thr Phe Arg His Asp Leu Lys Ile Tyr Ala
565 570 575

Ser Asp Glu Gly Arg Val Gln Met Thr Ala Ala Ala Phe Ala Lys Gly
580 585 590

Leu Leu Ala Leu Glu Gly Glu Leu Thr Pro Ile Leu Val Gln Met Val
595 600 605

Lys Ser Ala Asn Met Asn Gly Leu Leu Asp Ser Asp Gly Asp Ser Leu
610 615 620

Ser Ser Cys Gln His Arg Val Lys Ala Arg Leu His His Ile Leu Gln
625 630 635 640

Gln Asp Ala Pro Phe Gly Pro Glu Asp Tyr Asp Gln Leu Ala Pro Thr
645 650 655

Arg Ser Thr Ser Leu Leu Asn Ser Met Thr Ile Ile Gln Asn Pro Val
660 665 670

```
Lys Val Cys Asp Gln Val Phe Ala Leu Ile Glu Asn Leu Thr His Gln
        675                 680                 685

Ile Arg Glu Arg Met Gln Asp Pro Arg Ser Val Asp Leu Gln Leu Tyr
    690                 695                 700

His Ser Glu Thr Leu Glu Leu Met Leu Gln Arg Trp Ser Lys Leu Glu
705                 710                 715                 720

Arg Asp Phe Arg Gln Lys Ser Gly Arg Tyr Asp Ile Ser Lys Ile Pro
                725                 730                 735

Asp Ile Tyr Asp Cys Val Lys Tyr Asp Val Gln His Asn Gly Ser Leu
            740                 745                 750

Gly Leu Gln Gly Thr Ala Glu Leu Leu Arg Leu Ser Lys Ala Leu Ala
        755                 760                 765

Asp Val Val Ile Pro Gln Glu Tyr Gly Ile Ser Arg Glu Glu Lys Leu
    770                 775                 780

Glu Ile Ala Val Gly Phe Cys Leu Pro Leu Leu Arg Lys Ile Leu Leu
785                 790                 795                 800

Asp Leu Gln Arg Thr His Glu Asp Glu Ser Val Asn Lys Leu His Pro
                805                 810                 815

Leu Tyr Ser Arg Gly Val Leu Ser Pro Gly Arg His Val Arg Thr Arg
            820                 825                 830

Leu Tyr Phe Thr Ser Glu Ser His Val His Ser Leu Leu Ser Val Phe
        835                 840                 845

Arg Tyr Gly Gly Leu Leu Asp Glu Thr Gln Asp Ala Gln Trp Gln Arg
    850                 855                 860

Ala Leu Asp Tyr Leu Ser Ala Ile Ser Glu Leu Asn Tyr Met Thr Gln
865                 870                 875                 880

Ile Val Ile Met Leu Tyr Glu Asp Asn Thr Gln Asp Pro Leu Ser Glu
                885                 890                 895

Glu Arg Phe His Val Glu Leu His Phe Ser Pro Gly Val Lys Gly Val
            900                 905                 910
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Glu Glu Glu Gly Ser Ala Pro Ala Gly Cys Gly Phe Arg Pro Ala Ser
        915                 920                 925

Ser Glu Asn Glu Glu Met Lys Thr Asn Gln Gly Ser Met Glu Asn Leu
    930                 935                 940

Cys Pro Gly Lys Ala Ser Asp Glu Pro Asp Arg Ala Leu Gln Thr Ser
945                 950                 955                 960

Pro Gln Pro Pro Glu Gly Pro Gly Leu Pro Arg Arg Ser Pro Leu Ile
                965                 970                 975

Arg Asn Arg Lys Ala Gly Ser Met Glu Val Leu Ser Glu Thr Ser Ser
            980                 985                 990

Ser Arg Pro Gly Gly Tyr Arg Leu  Phe Ser Ser Ser Arg  Pro Pro Thr
        995                 1000                1005

Glu Met  Lys Gln Ser Gly Leu  Gly Ser Gln Cys Thr  Gly Leu Phe
    1010                1015                1020

Ser Thr  Thr Val Leu Gly Gly  Ser Ser Ser Ala Pro  Asn Leu Gln
    1025                1030                1035

Asp Tyr  Ala Arg Ser His Gly  Lys Lys Leu Pro Pro  Ala Ser Leu
    1040                1045                1050

Lys His  Arg Asp Glu Leu Leu  Glu Ser Thr Asn Thr  Lys Leu Trp
    1055                1060                1065

Pro Leu  Lys Leu Thr Leu Glu  Val Ala Ala Trp Phe  Ile Leu Leu
    1070                1075                1080

Ile Phe  Ile Leu Glu Ile Leu  Leu Lys Trp Leu Ser  Asn Phe Ser
    1085                1090                1095

Val Phe  Trp Lys Ser Ala Trp  Asn Val Phe Asp Phe  Val Val Thr
    1100                1105                1110

Met Leu  Val Arg Ile Glu Ile  Leu Arg Val Arg Leu  Val Gly
    1115                1120                1125
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<210> 359
<211> 55
<212> PRT
<213> Homo sapien

<400> 359

Arg Val Thr Val Leu Phe Ser Ser Phe Phe Phe Ser Leu Gln Gln Thr
1 5 10 15

Val Cys Gly Phe Asp Leu Leu Arg Ala Asn Gly His Ser Phe Val Cys
20 25 30

Asp Val Asn Gly Phe Ser Phe Val Lys Asn Ser Met Lys Tyr Tyr Asp
35 40 45

Asp Cys Ala Lys Ile Leu Gly
50 55

<210> 360
<211> 72
<212> PRT
<213> Homo sapien

<400> 360

Lys Gly Thr Gly His Glu His Ala Val His Gly Glu Pro Gly Pro His
1 5 10 15

Pro Leu Ala Gly Thr Ala Leu Gln Glu Val Gly Arg Pro Pro Pro Ala
20 25 30

Phe Pro Ser His Trp Pro Thr Ala Pro Gly Cys Val His His Ser Pro
35 40 45

Gly Ile Leu His Thr Gly Val Pro Pro Tyr Leu Thr Phe Leu Ser Cys
50 55 60

Leu Leu Ser Leu Pro Phe Gly Ile
65 70

<210> 361
<211> 91
<212> PRT
<213> Homo sapien

<400> 361

Phe Leu Pro Asp Ala Cys Gly Leu Ser Asp Val Ala His Val Glu Ser
1 5 10 15

Leu Gln Glu Lys Ser Gln Cys Ala Leu Glu Glu Tyr Val Arg Ser Gln
20 25 30

Tyr Pro Asn Gln Pro Thr Arg Phe Gly Lys Leu Leu Leu Arg Leu Pro
35 40 45

Ser Leu Arg Thr Val Ser Ser Ser Val Ile Glu Gln Leu Phe Phe Val
50 55 60

Arg Leu Val Gly Lys Thr Pro Ile Glu Thr Leu Ile Arg Asp Met Leu
65 70 75 80

Leu Ser Gly Ser Ser Phe Asn Trp Pro Tyr Met
85 90

<210> 362
<211> 273
<212> PRT
<213> Homo sapien

<400> 362

Met Gly Arg Ser Arg Ser Arg Ser Ser Ser Arg Ser Lys His Thr Lys
1 5 10 15

Ser Ser Lys His Asn Lys Lys Arg Ser Arg Ser Arg Ser Arg Ser Arg
20 25 30

Asp Lys Glu Arg Val Arg Lys Arg Ser Lys Ser Arg Glu Ser Lys Arg
35 40 45

Asn Arg Arg Arg Glu Ser Arg Ser Arg Ser Arg Ser Thr Asn Thr Ala
50 55 60

Val Ser Arg Arg Glu Arg Asp Arg Glu Arg Ala Ser Ser Pro Pro Asp
65 70 75 80

Arg Ile Asp Ile Phe Gly Arg Thr Val Ser Lys Arg Ser Ser Leu Asp
85 90 95

Glu Lys Gln Lys Arg Glu Glu Glu Glu Lys Lys Ala Glu Phe Glu Arg
100 105 110

Gln Arg Lys Ile Arg Gln Gln Glu Ile Glu Glu Lys Leu Ile Glu Glu
115 120 125

Glu Thr Ala Arg Arg Val Glu Glu Leu Val Ala Lys Arg Val Glu Glu
130 135 140

Glu Leu Glu Lys Arg Lys Asp Glu Ile Glu Arg Glu Val Leu Arg Arg
145 150 155 160

Val Glu Glu Ala Lys Arg Ile Met Glu Lys Gln Leu Leu Glu Glu Leu
165 170 175

Glu Arg Gln Arg Gln Ala Glu Leu Ala Ala Gln Lys Ala Arg Glu Val
180 185 190

Thr Leu Gly Arg Leu Glu Ser Arg Asp Ser Pro Trp Gln Asn Phe Gln
195 200 205

Cys Trp Val Leu Pro Pro Ala Gln Phe Arg Lys Arg Trp Asn Thr Asp
210 215 220

Tyr Leu Ile Pro Phe Ser Ser Lys Leu Asn Ile Ala Ala Lys Val Asn
225 230 235 240

Phe Leu Ala Tyr Ser Glu Val Leu Thr Asp Asn Leu Lys Val Gly Ser
245 250 255

Phe Tyr Lys Thr Tyr Ser Arg Ile Leu Phe Asp Leu Met Glu Leu Ala
260 265 270

Ile

<210> 363
<211> 142
<212> PRT
<213> Homo sapien

<400> 363

Met Lys Leu Asn Glu Lys Phe Ser Glu Gly Trp Arg Lys Pro Asn Ala
1 5 10 15

Ser Trp Lys Ser Ser Cys Ser Lys Asn Ser Ser Asp Arg Asp Lys Leu
20 25 30

Ser Leu Pro His Lys Lys Leu Glu Arg Gly Ser Trp Arg Val Trp Gln
35 40 45

Pro Arg Ser Thr Leu Cys Arg Thr Leu Asp Lys Thr Glu Glu Glu Arg
50 55 60

Ala Lys Arg Glu Glu Leu Glu Arg Ile Leu Glu Glu Asn Asn Arg Lys
65 70 75 80

Ile Ala Glu Ala Gln Ala Lys Leu Ala Glu Glu Gln Leu Arg Ile Val
85 90 95

Glu Glu Gln Arg Lys Ile His Glu Glu Arg Met Lys Leu Glu Gln Glu
100 105 110

Arg Gln Arg Gln Gln Lys Glu Glu Gln Lys Ile Ile Leu Gly Lys Gly
115 120 125

Lys Ser Arg Pro Lys Leu Ser Phe Ser Leu Lys Thr Gln Asp
130 135 140

<210> 364
<211> 102
<212> PRT
<213> Homo sapien

<400> 364

Met Ser Leu Lys Ser Ala Thr Lys Trp Gly Arg Arg Cys Asn Tyr Tyr
1 5 10 15

Tyr Gln His Leu Glu Ser Ile Met Asn Leu Leu Glu Tyr Phe Leu Ala
20 25 30

Leu Thr Ser Phe Ile Leu Arg Cys Ser Tyr Trp Ile Phe Pro Ser Ala
35 40 45

Asn Asn Met Glu Val Pro Ile Gln Gly Gln Ile Ile Pro Gly Phe Ile
50 55 60

Trp Ser Cys Leu Lys Val Lys Ser Leu Glu Phe Leu Met Ile Pro Phe
65 70 75 80

Leu Tyr Gly Leu Gln Phe Asp Arg Trp Glu Phe Ser Thr Leu Lys Lys
85 90 95

Val Ile Asn Gly Lys Met
100

<210> 365
<211> 92
<212> PRT
<213> Homo sapien

<400> 365

Leu Ser Ser Gln Leu His Gly Cys Ile Ser Val Gly Thr Gln Ala Ser
1 5 10 15

Pro Gly Tyr Leu Ser Cys Ser Cys Arg Leu Pro Pro Gly Leu Arg Arg
20 25 30

Gly Ala Pro Asp Pro Gly Ile Val Arg Leu Arg Pro Ala Lys Glu Gly
35 40 45

Pro Ala Gly Gly Ala Pro Ala Gly Val Ser Cys Leu Ala Ala Gly Arg
50 55 60

Gly Asp Leu Glu Asp Arg Val Lys Leu Gln Lys Thr Trp Gly Gly Met
65 70 75 80

Ala Arg Glu Asp Ala Lys Asp Trp Gly Arg Gly Ser
85 90

<210> 366
<211> 160
<212> PRT
<213> Homo sapien

<400> 366

Met Ser Leu Lys Ser Ala Thr Lys Trp Gly Arg Arg Cys Asn Tyr Tyr
1 5 10 15

Tyr Gln His Leu Glu Ser Ile Met Asn Leu Leu Glu Tyr Phe Leu Ala
20 25 30

Leu Thr Ser Phe Ile Leu Arg Cys Ser Tyr Trp Ile Phe Pro Ser Ala
35 40 45

Asn Asn Met Glu Val Pro Ile Gln Gly Gln Ile Ile Pro Gly Phe Ile
50 55 60

Trp Ser Cys Leu Lys Val Lys Ser Leu Glu Phe Leu Met Ile Pro Phe
65 70 75 80

Leu Tyr Gly Leu Gln Phe Asp Arg Trp Glu Phe Ser Thr Leu Lys Lys
85 90 95

Thr Leu Leu Leu Ser Gly Asn Pro Cys Pro Pro Leu Thr Ser Thr Gln
100 105 110

Asn Cys Phe Pro His Ser Leu Thr Ala Arg Val Val Lys Asn Trp Asp
115 120 125

Val Leu Leu Arg Trp Ala Val Glu Cys His Thr Glu Ser Arg Ser Leu

130 135 140

Gly Val Ser Leu Cys Cys Pro Gly Trp Ser Thr Glu Val Ala Val Asn
145 150 155 160

<210> 367
<211> 119
<212> PRT
<213> Homo sapien

<400> 367

Ser Ser Lys Val Ser Arg Asp Thr Leu Tyr Glu Ala Val Arg Glu Val
1 5 10 15

Leu His Gly Asn Gln Arg Gln Arg Arg Lys Phe Leu Glu Thr Val Glu
20 25 30

Leu Gln Ile Ser Leu Lys Asn Tyr Asp Pro Gln Lys Asp Lys Arg Phe
35 40 45

Ser Gly Thr Val Arg Leu Lys Ser Thr Pro Arg Pro Lys Phe Ser Val
50 55 60

Cys Val Leu Gly Asp Gln Gln His Cys Asp Glu Ala Lys Ala Val Asp
65 70 75 80

Ile Pro His Met Asp Ile Glu Ala Leu Lys Lys Leu Asn Lys Asn Lys
85 90 95

Lys Leu Val Lys Lys Leu Ala Lys Lys Tyr Asp Ala Phe Leu Ala Ser
100 105 110

Glu Ser Leu Ile Lys Gln Ile
115

<210> 368
<211> 59
<212> PRT
<213> Homo sapien

<400> 368

Met Ser Ser Lys Val Ser Arg Asp Thr Leu Tyr Glu Ala Val Arg Glu
1 5 10 15

Val Leu His Gly Asn Gln Arg Lys Ala Ala Arg Lys Phe Leu Glu Thr
20 25 30

Val Glu Leu Gln Ile Ser Leu Lys Asn Tyr Asp Pro Gln Lys Asp Lys
35 40 45

Arg Phe Ser Gly Thr Val Arg Leu Ala Pro Phe
50 55

<210> 369
<211> 110
<212> PRT
<213> Homo sapien

<400> 369

Met Arg Glu Ala Arg His Cys Lys Leu Thr Ser Gln Val Leu Val Asn
1 5 10 15

Tyr Asp Leu Glu Ile Phe Thr Leu Arg Cys Leu Gly Ser Gly Ile Arg
20 25 30

Leu Leu Leu Gln Val Gly Ser Arg His Ser Gln Leu Ser Arg Val Gln
35 40 45

Gly Pro Gln Leu Arg Asn Arg Gln Asn Ser Ser Pro Gly Ser Leu Asp
50 55 60

Gln Ser Ile Arg Cys Thr Ala Val Met Pro Trp Ile Met Gly Gln Pro
65 70 75 80

Gly Phe Leu Arg Ala Cys Phe Gly Thr Ser Glu Gly Pro Glu Asp Phe
85 90 95

Leu Glu Thr Val Trp Ala Arg Glu Lys Thr Glu Ala Gly Ser
100 105 110

<210> 370
<211> 61
<212> PRT
<213> Homo sapien

<400> 370

Lys Gly Pro Thr Gly Ala Pro Arg Val Arg Pro Tyr Tyr Thr Val Leu
1 5 10 15

Ser Ser Asp His Glu Gln Gln Ser Leu Ser Arg His Pro Val Arg Gly
20 25 30

Gly Ala Gly Ser Pro Ala Arg Glu Pro Ala Gln Gly Cys Ser Gln Val
35 40 45

Pro Gly Asp Gly Gly Val Ala Asp Gln Leu Glu Glu Leu
50 55 60

<210> 371
<211> 402
<212> PRT
<213> Homo sapien

<400> 371

Met Leu Ser Pro Gln Arg Ala Leu Leu Cys Asn Leu Asn His Ile His
1 5 10 15

Leu Gln His Val Ser Leu Gly Leu His Leu Ser Arg Arg Pro Glu Leu
20 25 30

Gln Glu Gly Pro Leu Ser Thr Pro Pro Pro Pro Gly Asp Thr Gly Gly
35 40 45

Lys Glu Ser Arg Gly Pro Cys Ser Gly Thr Leu Val Asp Ala Asn Ser
50 55 60

Asn Ser Pro Ala Val Pro Cys Arg Cys Cys Gln Glu His Gly Pro Gly
65 70 75 80

Leu Glu Asn Arg Gln Asp Pro Ser Gln Glu Glu Glu Gly Ala Ala Ser
85 90 95

Pro Ser Asp Pro Gly Cys Ser Ser Ser Leu Ser Ser Cys Ser Asp Leu
100 105 110

Ser Pro Asp Glu Ser Pro Val Ser Val Tyr Leu Arg Asp Leu Pro Gly
115 120 125

Asp Glu Asp Ala His Pro Gln Pro Ser Ile Ile Pro Leu Glu Gln Gly
130 135 140

Ser Pro Leu Ala Ser Ala Gly Pro Gly Thr Cys Ser Pro Asp Ser Phe
145 150 155 160

Cys Cys Ser Pro Asp Ser Cys Ser Gly Ala Ser Ser Ser Pro Asp Pro
165 170 175

Gly Leu Asp Ser Asn Cys Asn Ala Leu Thr Thr Cys Gln Asp Val Pro
180 185 190

Ser Pro Gly Leu Glu Glu Glu Asp Glu Arg Ala Glu Gln Asp Leu Pro

195 200 205

Thr Ser Glu Leu Leu Glu Ala Asp Asp Gly Lys Ile Asp Ala Gly Lys
210 215 220

Thr Glu Pro Ser Trp Lys Ile Asn Pro Ile Trp Lys Ile Asp Thr Glu
225 230 235 240

Lys Thr Lys Ala Glu Trp Lys Thr Thr Glu Asn Asn Asn Thr Gly Trp
245 250 255

Lys Asn Asn Gly Asn Val Asn Ser Ser Trp Lys Ser Glu Pro Glu Lys
260 265 270

Phe Asp Ser Gly Trp Lys Thr Asn Thr Arg Ile Thr Asp Ser Gly Ser
275 280 285

Lys Thr Asp Ala Gly Lys Ile Asp Gly Gly Trp Arg Ser Asp Val Ser
290 295 300

Glu Glu Pro Val Pro His Arg Thr Ile Thr Ser Phe His Glu Leu Ala
305 310 315 320

Gln Lys Arg Lys Arg Gly Pro Gly Leu Pro Leu Val Pro Gln Ala Lys
325 330 335

Lys Asp Arg Ser Asp Trp Leu Ile Val Phe Ser Pro Asp Thr Glu Leu
340 345 350

Pro Pro Ser Gly Ser Pro Gly Gly Ser Ser Ala Pro Pro Arg Glu Val
355 360 365

Thr Thr Phe Lys Glu Leu Arg Ser Arg Ser Arg Ala Pro Ala Pro Pro
370 375 380

Val Pro Pro Arg Asp Pro Pro Val Gly Trp Ala Leu Val Pro Pro Arg
385 390 395 400

Pro Pro

<210> 372
<211> 243
<212> PRT
<213> Homo sapien

<400> 372

```
Met Met Pro Leu Ser Arg Trp Leu Arg Ser Val Gly Val Phe Leu Leu
1               5                  10                  15

Pro Ala Pro Tyr Trp Ala Pro Arg Glu Arg Trp Leu Gly Ser Leu Arg
            20                  25                  30

Arg Pro Ser Leu Val His Gly Tyr Pro Val Leu Ala Trp His Ser Ala
        35                  40                  45

Arg Cys Trp Cys Gln Ala Trp Thr Glu Glu Pro Arg Ala Leu Cys Ser
    50                  55                  60

Ser Leu Arg Met Asn Gly Asp Gln Asn Ser Asp Val Tyr Ala Gln Glu
65                  70                  75                  80

Lys Gln Asp Phe Val Gln His Phe Ser Gln Ile Val Arg Val Leu Thr
                85                  90                  95

Glu Asp Glu Met Gly His Pro Glu Ile Gly Asp Ala Ile Ala Arg Leu
            100                 105                 110

Lys Glu Val Leu Glu Tyr Asn Ala Ile Gly Gly Lys Tyr Asn Arg Gly
        115                 120                 125

Leu Thr Val Val Val Ala Phe Arg Glu Leu Val Glu Pro Arg Lys Gln
    130                 135                 140

Asp Ala Asp Ser Leu Gln Arg Ala Trp Thr Val Gly Trp Cys Val Glu
145                 150                 155                 160

Leu Leu Gln Ala Phe Phe Leu Val Ala Asp Asp Ile Met Asp Ser Ser
                165                 170                 175

Leu Thr Arg Arg Gly Gln Ile Cys Trp Tyr Gln Lys Pro Gly Val Gly
            180                 185                 190

Leu Asp Ala Ile Asn Asp Ala Asn Leu Leu Glu Ala Cys Ile Tyr Arg
        195                 200                 205

Leu Leu Lys Leu Tyr Cys Arg Glu Gln Pro Tyr Tyr Leu Asn Leu Ile
    210                 215                 220

Glu Leu Phe Leu Gln Val Tyr Cys Arg Gln Gly Pro Met Pro Arg Gly
225                 230                 235                 240
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Cys Pro Trp

<210> 373
<211> 380
<212> PRT
<213> Homo sapien

<400> 373

Met Tyr Phe Asp Trp Gly Pro Gly Glu Met Leu Val Cys Glu Thr Ser
1 5 10 15

Phe Asn Lys Lys Glu Lys Ser Glu Met Val Pro Ser Cys Pro Phe Ile
20 25 30

Tyr Ile Ile Arg Lys Asp Val Asp Val Tyr Ser Gln Ile Leu Arg Lys
35 40 45

Leu Phe Asn Glu Ser His Gly Ile Phe Leu Gly Leu Gln Arg Ile Asp
50 55 60

Glu Glu Leu Thr Gly Lys Ser Arg Lys Ser Gln Leu Val Arg Val Ser
65 70 75 80

Lys Asn Tyr Arg Ser Val Ile Arg Ala Cys Met Glu Glu Met His Gln
85 90 95

Val Ala Ile Ala Ala Lys Asp Pro Ala Asn Gly Arg Gln Phe Ser Ser
100 105 110

Gln Val Ser Ile Leu Ser Ala Met Glu Leu Ile Trp Asn Leu Cys Glu
115 120 125

Ile Leu Phe Ile Glu Val Ala Pro Ala Gly Pro Leu Leu Leu His Leu
130 135 140

Leu Asp Trp Val Arg Leu His Val Cys Glu Val Asp Ser Leu Ser Ala
145 150 155 160

Asp Val Leu Gly Ser Glu Asn Pro Ser Lys His Asp Ser Phe Trp Asn
165 170 175

Leu Val Thr Ile Leu Val Leu Gln Gly Arg Leu Asp Glu Ala Arg Gln
180 185 190

Met Leu Ser Lys Glu Ala Asp Ala Ser Pro Ala Ser Ala Gly Ile Cys
195 200 205

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Arg Ile Met Gly Asp Leu Met Arg Thr Met Pro Ile Leu Ser Pro Gly
    210                 215                 220

Asn Thr Gln Thr Leu Thr Glu Leu Glu Leu Lys Trp Gln His Trp His
225                 230                 235                 240

Glu Glu Cys Glu Arg Tyr Leu Gln Asp Ser Thr Phe Ala Thr Ser Pro
                245                 250                 255

His Leu Glu Ser Leu Leu Lys Ile Met Leu Gly Asp Glu Ala Ala Leu
            260                 265                 270

Leu Glu Gln Lys Glu Leu Leu Ser Asn Trp Tyr His Phe Leu Val Thr
        275                 280                 285

Arg Leu Leu Tyr Ser Asn Pro Thr Val Lys Pro Ile Asp Leu His Tyr
    290                 295                 300

Tyr Ala Gln Ser Ser Leu Asp Leu Phe Leu Gly Gly Glu Ser Ser Pro
305                 310                 315                 320

Glu Pro Leu Asp Asn Ile Leu Leu Ala Ala Phe Glu Phe Asp Ile His
                325                 330                 335

Gln Val Ile Lys Glu Cys Arg Asn Lys Thr Asp Leu Ser Arg Arg Ser
            340                 345                 350

Leu Leu Asp Ala Gly Ser Ile Lys Gly Glu Ser Ile Leu Leu Phe Pro
        355                 360                 365

Val Ala Glu Glu Lys Glu Lys Tyr His Glu Glu Gly
    370                 375                 380
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<210> 374
<211> 679
<212> PRT
<213> Homo sapien

<400> 374

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Met Tyr Phe Asp Trp Gly Pro Gly Glu Met Leu Val Cys Glu Thr Ser
1               5                   10                  15

Phe Asn Lys Lys Glu Lys Ser Glu Met Val Pro Ser Cys Pro Phe Ile
            20                  25                  30
```

Tyr Ile Ile Arg Lys Asp Val Asp Val Tyr Ser Gln Ile Leu Arg Lys
35 40 45

Leu Phe Asn Glu Ser His Gly Ile Phe Leu Gly Leu Gln Arg Ile Asp
50 55 60

Glu Glu Leu Thr Gly Lys Ser Arg Lys Ser Gln Leu Val Arg Val Ser
65 70 75 80

Lys Asn Tyr Arg Ser Val Ile Arg Ala Cys Met Glu Glu Met His Gln
85 90 95

Val Ala Ile Ala Ala Lys Asp Pro Ala Asn Gly Arg Gln Phe Ser Ser
100 105 110

Gln Val Ser Ile Leu Ser Ala Met Glu Leu Ile Trp Asn Leu Cys Glu
115 120 125

Ile Leu Phe Ile Glu Val Ala Pro Ala Gly Pro Leu Leu Leu His Leu
130 135 140

Leu Asp Trp Val Arg Leu His Val Cys Glu Val Asp Ser Leu Ser Ala
145 150 155 160

Asp Val Leu Gly Ser Glu Asn Pro Ser Lys His Asp Ser Phe Trp Asn
165 170 175

Leu Val Thr Ile Leu Val Leu Gln Gly Arg Leu Asp Glu Ala Arg Gln
180 185 190

Met Leu Ser Lys Glu Ala Asp Ala Ser Pro Ala Ser Ala Gly Ile Cys
195 200 205

Arg Ile Met Gly Asp Leu Met Arg Thr Met Pro Ile Leu Ser Pro Gly
210 215 220

Asn Thr Gln Thr Leu Thr Glu Leu Glu Leu Lys Trp Gln His Trp His
225 230 235 240

Glu Glu Cys Glu Arg Tyr Leu Gln Asp Ser Thr Phe Ala Thr Ser Pro
245 250 255

His Leu Glu Ser Leu Leu Lys Ile Met Leu Gly Asp Glu Ala Ala Leu
260 265 270

Leu Glu Gln Lys Glu Leu Leu Ser Asn Trp Tyr His Phe Leu Val Thr

275 280 285

Arg Leu Leu Tyr Ser Asn Pro Thr Val Lys Pro Ile Asp Leu His Tyr
290 295 300

Tyr Ala Gln Ser Ser Leu Asp Leu Phe Leu Gly Gly Glu Ser Ser Pro
305 310 315 320

Glu Pro Leu Asp Asn Ile Leu Leu Ala Ala Phe Glu Phe Asp Ile His
325 330 335

Gln Val Ile Lys Glu Cys Ser Phe Leu Leu Lys Thr Gly Gln Phe Leu
340 345 350

Ala Val Trp Gln Glu Glu Thr Ala Gly Val His Phe Thr Gly Ser Trp
355 360 365

Ala Arg Cys Arg Gln Phe Pro Gly Ala Leu Gln Val Leu Gln Lys Tyr
370 375 380

Arg Ala Lys Ser Ile Ala Leu Ser Asn Trp Trp Phe Val Ala His Leu
385 390 395 400

Thr Asp Leu Leu Asp His Cys Lys Leu Leu Gln Ser His Asn Leu Tyr
405 410 415

Phe Gly Ser Asn Met Arg Glu Phe Leu Leu Leu Glu Tyr Ala Ser Gly
420 425 430

Leu Phe Ala His Pro Ser Leu Trp Gln Leu Gly Val Asp Tyr Phe Asp
435 440 445

Tyr Cys Pro Glu Leu Gly Arg Val Ser Leu Glu Leu His Ile Glu Arg
450 455 460

Ile Pro Leu Asn Thr Glu Gln Lys Ala Leu Lys Val Leu Arg Ile Cys
465 470 475 480

Glu Gln Arg Gln Met Thr Glu Gln Val Arg Ser Ile Cys Lys Ile Leu
485 490 495

Ala Met Lys Ala Val Arg Asn Asn Arg Leu Gly Ser Ala Leu Ser Trp
500 505 510

Ser Ile Arg Ala Lys Asp Ala Ala Phe Ala Thr Leu Val Ser Asp Arg
515 520 525

Phe Leu Arg Asp Tyr Cys Glu Arg Gly Cys Phe Ser Asp Leu Asp Leu
530 535 540

Ile Asp Asn Leu Gly Pro Ala Met Met Leu Ser Asp Arg Leu Thr Phe
545 550 555 560

Leu Gly Lys Tyr Arg Glu Phe His Arg Met Tyr Gly Glu Lys Arg Phe
565 570 575

Ala Asp Ala Ala Ser Leu Leu Leu Ser Leu Met Thr Ser Arg Ile Ala
580 585 590

Pro Arg Ser Phe Trp Met Thr Leu Leu Thr Asp Ala Leu Pro Leu Leu
595 600 605

Glu Gln Lys Gln Val Ile Phe Ser Ala Glu Gln Thr Tyr Glu Leu Met
610 615 620

Arg Cys Leu Glu Asp Leu Thr Ser Arg Arg Pro Val His Gly Glu Ser
625 630 635 640

Asp Thr Glu Gln Leu Gln Asp Asp Asp Ile Glu Thr Thr Lys Val Glu
645 650 655

Met Leu Arg Leu Ser Leu Ala Arg Asn Leu Ala Arg Ala Ile Ile Arg
660 665 670

Glu Gly Ser Leu Glu Gly Ser
675

<210> 375
<211> 124
<212> PRT
<213> Homo sapien

<400> 375

Met Val Pro Ser Cys Pro Phe Ile Tyr Ile Ile Arg Lys Asp Val Asp
1 5 10 15

Val Tyr Ser Gln Ile Leu Arg Lys Leu Phe Asn Glu Ser His Gly Ile
20 25 30

Phe Leu Gly Leu Gln Arg Ile Asp Glu Glu Leu Thr Gly Lys Ser Arg
35 40 45

Lys Ser Gln Leu Val Arg Val Ser Lys Asn Tyr Arg Ser Val Ile Arg
50 55 60

Ala Cys Met Glu Glu Met His Gln Val Ala Ile Ala Ala Lys Asp Pro
65 70 75 80

Ala Asn Gly Arg Gln Phe Ser Ser Gln Val Ser Ile Leu Ser Ala Met
85 90 95

Glu Leu Ile Trp Asn Leu Cys Glu Ile Leu Phe Ile Glu Val Ala Pro
100 105 110

Gly Arg His Gly Ile Ser His His Asn Leu Ile Gly
115 120

<210> 376
<211> 95
<212> PRT
<213> Homo sapien

<400> 376

Lys Lys Lys Lys Lys Lys Asn Lys Lys Gln Lys Ile His His Asn Lys
1 5 10 15

Arg Pro Asn Val Asn Lys Asp Glu Gly Arg Arg Gly Val Ala Val Ala
20 25 30

Glu Arg Arg Gln Arg Arg Ser Thr Glu Gly Leu Gly Leu Gln Ala Leu
35 40 45

Gln Glu Thr Pro Arg Arg Ser Leu Val Ser Gln Pro Ala Leu Ser Gly
50 55 60

Arg Pro Glu Arg Glu Ala Leu Ala Ser Glu Arg Leu Leu Gly Ala Trp
65 70 75 80

Gly Ser Ala Leu Trp Arg Ser Ser Met Ala Ser Gln Gln Ser Leu
85 90 95

<210> 377
<211> 68
<212> PRT
<213> Homo sapien

<400> 377

Met Ser Pro Arg Cys Ser Ser His Ala Ala Ala Arg Leu Tyr Asp Arg
1 5 10 15

Ala Pro His Asp Ala Gln Ile Arg Arg Gly Cys Ser Leu Glu Gly Glu
20 25 30

Ser Val Cys Arg Gly His Pro Arg Pro His Gly Cys Trp Gly Leu Thr
35 40 45

Gly Arg Val Arg Ala Ser Gly Arg Gly Arg Ala Gly Arg Asp Ser Pro
50 55 60

Ala Leu Thr Pro
65

<210> 378
<211> 190
<212> PRT
<213> Homo sapien

<400> 378

Ser Val Ala Asn Met Gln Leu Phe Val Arg Ala Gln Glu Leu His Thr
1 5 10 15

Phe Glu Val Thr Gly Gln Glu Thr Val Ala Gln Ile Lys Ala His Val
20 25 30

Ala Ser Leu Glu Gly Ile Ala Pro Glu Asp Gln Val Val Leu Leu Ala
35 40 45

Gly Ala Pro Leu Glu Asp Glu Ala Thr Leu Gly Gln Cys Gly Val Glu
50 55 60

Ala Leu Thr Thr Leu Glu Val Ala Gly Arg Met Leu Gly Gly Lys Val
65 70 75 80

His Gly Ser Leu Ala Arg Ala Gly Lys Val Arg Gly Gln Thr Pro Lys
85 90 95

Val Ser Glu Ser Ile Ser Gly His Gly Val Arg Thr Phe Phe Pro Phe
100 105 110

Thr Ala Lys Pro Ser Pro Trp Ala Leu Thr Arg Phe Ala Phe Ser Leu
115 120 125

Pro Gly Asp Glu Pro Glu Gly Arg Asp Ala Arg Cys Gly Arg Gln Glu
130 135 140

Pro Gly Pro Asp Pro Ser Leu Leu Gln Val Ala Lys Lys Lys Lys Thr

145 150 155 160

Gly Arg Ala Lys Arg Arg Met Gln Tyr Asn Arg Arg Phe Val Asn Val
165 170 175

Val Pro Thr Phe Gly Lys Lys Lys Gly Pro Asn Ala Asn Ser
180 185 190

<210> 379
<211> 69
<212> PRT
<213> Homo sapien

<400> 379

Phe Lys Leu Leu Thr Met Tyr Gly Glu Gly Lys Val His Gly Ser Leu
1 5 10 15

Ala Arg Ala Gly Lys Val Arg Gly Gln Thr Pro Lys Val Ala Lys Gln
20 25 30

Glu Lys Lys Lys Lys Lys Thr Gly Arg Ala Lys Arg Arg Met Gln Tyr
35 40 45

Asn Arg Arg Phe Val Asn Val Val Pro Thr Phe Gly Lys Lys Lys Gly
50 55 60

Pro Asn Ala Asn Ser
65

<210> 380
<211> 295
<212> PRT
<213> Homo sapien

<400> 380

Met Glu Thr Pro Ala Trp Pro Arg Val Pro Arg Pro Glu Thr Ala Val
1 5 10 15

Ala Arg Thr Leu Leu Leu Gly Trp Val Phe Ala Gln Val Ala Gly Ala
20 25 30

Ser Gly Thr Thr Asn Thr Val Ala Ala Tyr Asn Leu Thr Trp Lys Ser
35 40 45

Thr Asn Phe Lys Thr Ile Leu Glu Trp Glu Pro Lys Pro Val Asn Gln
50 55 60

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Val Tyr Thr Val Gln Ile Ser Thr Lys Ser Gly Asp Trp Lys Ser Lys
65                  70                  75                  80

Cys Phe Tyr Thr Thr Asp Thr Glu Cys Asp Leu Thr Asp Glu Ile Val
                85                  90                  95

Lys Asp Val Lys Gln Thr Tyr Leu Ala Arg Val Phe Ser Tyr Pro Ala
            100                 105                 110

Gly Asn Val Glu Ser Thr Gly Ser Ala Gly Glu Pro Leu Tyr Glu Asn
        115                 120                 125

Ser Pro Glu Phe Thr Pro Tyr Leu Glu Thr Asn Leu Gly Gln Pro Thr
    130                 135                 140

Ile Gln Ser Phe Glu Gln Val Gly Thr Lys Val Asn Val Thr Val Glu
145                 150                 155                 160

Asp Glu Arg Thr Leu Val Arg Arg Asn Asn Thr Phe Leu Ser Leu Arg
                165                 170                 175

Asp Val Phe Gly Lys Asp Leu Ile Tyr Thr Leu Tyr Tyr Trp Lys Ser
            180                 185                 190

Ser Ser Ser Gly Lys Lys Thr Ala Lys Thr Asn Thr Asn Glu Phe Leu
        195                 200                 205

Ile Asp Val Asp Lys Gly Glu Asn Tyr Cys Phe Ser Val Gln Ala Val
    210                 215                 220

Ile Pro Ser Arg Thr Val Asn Arg Lys Ser Thr Asp Ser Pro Val Glu
225                 230                 235                 240

Cys Met Gly Gln Glu Lys Gly Glu Phe Arg Glu Ile Phe Tyr Ile Ile
                245                 250                 255

Gly Ala Val Val Phe Val Val Ile Ile Leu Val Ile Ile Leu Ala Ile
            260                 265                 270

Ser Leu His Lys Cys Arg Lys Ala Gly Val Gly Gln Ser Trp Lys Glu
        275                 280                 285

Asn Ser Pro Leu Asn Val Ser
    290                 295
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<210> 381

<211> 376
<212> PRT
<213> Homo sapien

<400> 381

Met Ala Asp Tyr Trp Lys Ser Gln Pro Lys Lys Phe Cys Asp Tyr Cys
1 5 10 15

Lys Cys Trp Ile Ala Asp Asn Arg Pro Ser Val Glu Phe His Glu Arg
20 25 30

Gly Lys Asn His Lys Glu Asn Val Ala Lys Arg Ile Ser Glu Ile Lys
35 40 45

Gln Lys Ser Leu Asp Lys Ala Lys Glu Glu Glu Lys Ala Ser Lys Glu
50 55 60

Phe Ala Ala Met Glu Ala Ala Ala Leu Lys Ala Tyr Gln Glu Asp Leu
65 70 75 80

Lys Arg Leu Gly Leu Glu Ser Glu Ile Leu Glu Pro Ser Ile Thr Pro
85 90 95

Val Thr Ser Thr Ile Pro Pro Thr Ser Thr Ser Asn Gln Gln Lys Glu
100 105 110

Lys Lys Asp Lys Lys Lys Arg Gln Lys Asp Pro Ser Lys Gly Arg Trp
115 120 125

Val Glu Gly Ile Thr Ser Glu Gly Tyr His Tyr Tyr Tyr Asp Leu Ile
130 135 140

Ser Gly Ala Ser Gln Trp Glu Lys Pro Glu Gly Phe Gln Gly Asp Leu
145 150 155 160

Lys Lys Thr Ala Val Lys Thr Val Trp Val Glu Gly Leu Ser Glu Asp
165 170 175

Gly Phe Thr Tyr Tyr Tyr Asn Thr Glu Thr Gly Glu Ser Arg Trp Glu
180 185 190

Lys Pro Asp Asp Phe Ile Pro His Thr Ser Asp Leu Pro Ser Ser Lys
195 200 205

Val Asn Glu Asn Ser Leu Gly Thr Leu Asp Glu Ser Lys Ser Ser Asp
210 215 220

Ser His Ser Asp Ser Asp Gly Glu Gln Glu Ala Glu Glu Gly Gly Val
225 230 235 240

Ser Thr Glu Thr Glu Lys Pro Lys Ile Lys Phe Gln Glu Lys Asn Lys
245 250 255

Asn Ser Asp Gly Gly Ser Asp Pro Glu Thr Gln Lys Glu Lys Ser Ile
260 265 270

Gln Lys Gln Asn Ser Leu Gly Ser Asn Glu Glu Lys Ser Lys Thr Leu
275 280 285

Lys Lys Ser Asn Pro Tyr Gly Glu Trp Gln Glu Ile Lys Gln Glu Val
290 295 300

Glu Ser His Glu Glu Val Asp Leu Glu Leu Pro Ser Thr Glu Asn Glu
305 310 315 320

Tyr Val Ser Thr Ser Glu Ala Asp Gly Gly Gly Glu Pro Lys Val Val
325 330 335

Phe Lys Glu Lys Thr Val Thr Ser Leu Gly Val Met Ala Asp Gly Val
340 345 350

Ala Pro Val Phe Lys Lys Arg Arg Thr Glu Asn Gly Lys Ser Arg Asn
355 360 365

Leu Arg Gln Arg Gly Asp Asp Gln
370 375

<210> 382
<211> 619
<212> PRT
<213> Homo sapien

<400> 382

Met Ala Ala Val Val Gln Gln Asn Asp Leu Val Phe Glu Phe Ala Ser
1 5 10 15

Asn Val Met Glu Asp Glu Arg Gln Leu Gly Asp Pro Ala Ile Phe Pro
20 25 30

Ala Val Ile Val Glu His Val Pro Gly Ala Asp Ile Leu Asn Ser Tyr
35 40 45

Ala Gly Leu Ala Cys Val Glu Glu Pro Ser Asp Met Ile Thr Glu Ser

50 55 60

Ser Leu Asp Val Ala Glu Glu Glu Ile Ile Asp Asp Asp Asp Asp Asp
65 70 75 80

Ile Thr Leu Thr Val Glu Ala Ser Cys His Asp Gly Asp Glu Thr Ile
85 90 95

Glu Thr Ile Glu Ala Ala Glu Ala Leu Leu Asn Met Asp Ser Pro Gly
100 105 110

Pro Met Leu Asp Glu Lys Arg Ile Asn Asn Asn Ile Phe Ser Ser Pro
115 120 125

Glu Asp Asp Met Val Val Ala Pro Val Thr His Val Ser Val Thr Leu
130 135 140

Asp Gly Ile Pro Glu Val Met Glu Thr Gln Gln Val Gln Glu Lys Tyr
145 150 155 160

Ala Asp Ser Pro Gly Ala Ser Ser Pro Glu Gln Pro Lys Arg Lys Lys
165 170 175

Gly Arg Lys Thr Lys Pro Pro Arg Pro Asp Ser Pro Ala Thr Thr Pro
180 185 190

Asn Ile Ser Val Lys Lys Lys Asn Lys Asp Gly Lys Gly Asn Thr Ile
195 200 205

Tyr Leu Trp Glu Phe Leu Leu Ala Leu Leu Gln Asp Lys Ala Thr Cys
210 215 220

Pro Lys Tyr Ile Lys Trp Thr Gln Arg Glu Lys Gly Ile Phe Lys Leu
225 230 235 240

Val Asp Ser Lys Ala Val Ser Arg Leu Trp Gly Lys His Lys Asn Lys
245 250 255

Pro Asp Met Asn Tyr Glu Thr Met Gly Arg Ala Leu Arg Tyr Tyr Tyr
260 265 270

Gln Arg Gly Ile Leu Ala Lys Val Glu Gly Gln Arg Leu Val Tyr Gln
275 280 285

Phe Lys Glu Met Pro Lys Asp Leu Ile Tyr Ile Asn Asp Glu Asp Pro
290 295 300

Ser Ser Ser Ile Glu Ser Ser Asp Pro Ser Leu Ser Ser Ser Ala Thr
305 310 315 320

Ser Asn Arg Asn Gln Thr Ser Arg Ser Arg Val Ser Ser Ser Pro Gly
325 330 335

Val Lys Gly Gly Ala Thr Ser Val Leu Lys Pro Gly Asn Ser Lys Ala
340 345 350

Ala Lys Pro Lys Asp Pro Val Glu Val Ala Gln Pro Ser Glu Val Leu
355 360 365

Arg Thr Val Gln Pro Thr Gln Ser Pro Tyr Pro Thr Gln Leu Phe Arg
370 375 380

Thr Val His Val Val Gln Pro Val Gln Ala Val Pro Glu Gly Glu Ala
385 390 395 400

Ala Arg Thr Ser Thr Met Gln Asp Glu Thr Leu Asn Ser Ser Val Gln
405 410 415

Ser Ile Arg Thr Ile Gln Ala Pro Thr Gln Val Pro Val Val Val Ser
420 425 430

Pro Arg Asn Gln Gln Leu His Thr Val Thr Leu Gln Thr Val Pro Leu
435 440 445

Thr Thr Val Ile Ala Ser Thr Asp Pro Ser Ala Gly Thr Gly Ser Gln
450 455 460

Lys Phe Ile Leu Gln Ala Ile Pro Ser Ser Gln Pro Met Thr Val Leu
465 470 475 480

Lys Glu Asn Val Met Leu Gln Ser Gln Lys Ala Gly Ser Pro Pro Ser
485 490 495

Ile Val Leu Gly Pro Ala Gln Val Gln Gln Val Leu Thr Ser Asn Val
500 505 510

Gln Thr Ile Cys Asn Gly Thr Val Ser Val Ala Ser Ser Pro Ser Phe
515 520 525

Ser Ala Thr Ala Pro Val Val Thr Phe Ser Pro Arg Ser Ser Gln Leu
530 535 540

Val Ala His Pro Pro Gly Thr Val Ile Thr Ser Val Ile Lys Thr Gln
545 550 555 560

Glu Thr Lys Thr Leu Thr Gln Glu Val Glu Lys Lys Glu Ser Glu Asp
565 570 575

His Leu Lys Glu Asn Thr Glu Lys Thr Glu Gln Gln Pro Gln Pro Tyr
580 585 590

Val Met Val Val Ser Ser Ser Asn Gly Phe Thr Ser Gln Val Ala Met
595 600 605

Lys Gln Asn Glu Leu Leu Glu Pro Asn Ser Phe
610 615

<210> 383
<211> 63
<212> PRT
<213> Homo sapien

<400> 383

Val Ile Asp Val Ile His Glu Val Ala His Ser Trp Phe Gly Asn Ala
1 5 10 15

Val Thr Asn Ala Thr Trp Glu Glu Met Trp Leu Ser Glu Gly Leu Ala
20 25 30

Thr Tyr Ala Gln Arg Arg Ile Thr Thr Glu Thr Tyr Gly Ala Ala Phe
35 40 45

Thr Cys Leu Glu Thr Ala Phe Arg Leu Asp Ala Leu His Arg Gln
50 55 60

<210> 384
<211> 190
<212> PRT
<213> Homo sapien

<400> 384

Ser Val Ala Asn Met Gln Leu Phe Val Arg Ala Gln Glu Leu His Thr
1 5 10 15

Phe Glu Val Thr Gly Gln Glu Thr Val Ala Gln Ile Lys Ala His Val
20 25 30

Ala Ser Leu Glu Gly Ile Ala Pro Glu Asp Gln Val Val Leu Leu Ala
35 40 45

Gly Ala Pro Leu Glu Asp Glu Ala Thr Leu Gly Gln Cys Gly Val Glu
50 55 60

Ala Leu Thr Thr Leu Glu Val Ala Gly Arg Met Leu Gly Gly Lys Val
65 70 75 80

His Gly Ser Leu Ala Arg Ala Gly Lys Val Arg Gly Gln Thr Pro Lys
85 90 95

Val Ser Glu Ser Ile Ser Gly His Gly Val Arg Thr Phe Phe Pro Phe
100 105 110

Thr Ala Lys Pro Ser Pro Trp Ala Leu Thr Arg Phe Ala Phe Ser Leu
115 120 125

Pro Gly Asp Glu Pro Glu Gly Arg Asp Ala Arg Cys Gly Arg Gln Glu
130 135 140

Pro Gly Pro Asp Pro Ser Leu Leu Gln Val Ala Lys Lys Lys Lys Thr
145 150 155 160

Gly Arg Ala Lys Arg Arg Met Gln Tyr Asn Arg Arg Phe Val Asn Val
165 170 175

Val Pro Thr Phe Gly Lys Lys Lys Gly Pro Asn Ala Asn Ser
180 185 190

<210> 385
<211> 305
<212> PRT
<213> Homo sapien

<400> 385

Gln Phe Leu Gly Arg Trp Phe Ser Ala Gly Leu Ala Ser Asn Ser Ser
1 5 10 15

Trp Leu Arg Glu Lys Lys Ala Ala Leu Ser Met Cys Lys Ser Val Val
20 25 30

Ala Pro Ala Thr Asp Gly Gly Leu Asn Leu Thr Ser Thr Phe Leu Arg
35 40 45

Lys Asn Gln Cys Glu Thr Arg Thr Met Leu Leu Gln Pro Ala Gly Ser
50 55 60

Leu Gly Ser Tyr Ser Tyr Arg Ser Pro Arg Glu Trp Gly Leu His Arg
65 70 75 80

Pro Pro Gly Pro Ser Leu Gly Ala Thr Leu Ala Gly Thr Thr Leu Gly
85 90 95

Gln Pro Pro Ala Ala Glu Ile His Gly Val Gly Gly Asp Gly Cys Pro
100 105 110

Thr Ser Val Arg Gly Lys Gly Gln Arg Thr Gln Gly Phe Pro His Ser
115 120 125

His Leu Gly Asn Gly Ser His Gly Glu Thr Ser Ser Leu Pro Val Leu
130 135 140

Ala Ala Thr Ser Ala Ala Ala Pro Gly Ile Leu Val Phe Ala Trp Leu
145 150 155 160

Pro Gln Ile Leu Val Trp Gly Gln Gly Ser Gln Ala Val Gln Ala Arg
165 170 175

Ala Gly His Trp Leu Glu Ser Ser Arg Val Gly Glu His Pro Gly Pro
180 185 190

Ala Glu Gly Leu Ser Ala Pro Lys Ala His Arg Cys Thr Pro Ser Leu
195 200 205

Lys Gln Arg Gly Leu Gly Gly Val Pro Asp Arg Val Val Ser Trp Val
210 215 220

Pro Arg Leu Gly Ser Thr Tyr Ser Val Ser Val Val Glu Thr Asp Tyr
225 230 235 240

Asp Gln Tyr Ala Leu Leu Tyr Ser Gln Gly Ser Lys Gly Pro Gly Glu
245 250 255

Asp Phe Arg Met Ala Thr Leu Tyr Ser Arg Thr Gln Thr Pro Arg Ala
260 265 270

Glu Leu Lys Glu Lys Phe Thr Ala Phe Cys Lys Ala Gln Gly Phe Thr
275 280 285

Glu Asp Thr Ile Val Phe Leu Pro Gln Thr Asp Lys Cys Met Thr Glu
290 295 300

Gln

305

<210> 386
<211> 25
<212> PRT
<213> Homo sapien

<400> 386

Met Thr Asn Thr Lys Gly Lys Arg Arg Cys Thr Gln Tyr Met Ser Ser
1 5 10 15

Arg Pro Phe Arg Lys Tyr Gly Val Val
20 25

<210> 387
<211> 361
<212> PRT
<213> Homo sapien

<400> 387

Thr Gly Ile Ser Leu Ala Ser Gln Leu Lys Val Pro Pro Tyr Ala Ser
1 5 10 15

Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys Glu Tyr Tyr Glu Pro Gln
20 25 30

His Arg Ile Cys Cys Ser Arg Cys Pro Pro Gly Thr Tyr Val Ser Ala
35 40 45

Lys Cys Ser Arg Ile Arg Asp Thr Val Cys Ala Thr Cys Ala Glu Asn
50 55 60

Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr Ile Cys Gln Leu Cys Arg
65 70 75 80

Pro Cys Asp Pro Val Met Gly Leu Glu Glu Ile Ala Pro Cys Thr Ser
85 90 95

Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro Gly Met Phe Cys Ala Ala
100 105 110

Trp Ala Leu Glu Cys Thr His Cys Glu Arg Leu Ser Asp Cys Pro Pro
115 120 125

Gly Thr Glu Ala Glu Leu Lys Asp Glu Val Gly Lys Gly Asn Asn His
130 135 140

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Cys Val Pro Cys Lys Ala Gly His Phe Gln Asn Thr Ser Ser Pro Ser
145                 150                 155                 160

Ala Leu Cys Gln Pro His Thr Arg Cys Glu Asn Gln Gly Leu Val Glu
                165                 170                 175

Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr Thr Cys Lys Asn Pro Leu
            180                 185                 190

Glu Pro Leu Pro Pro Glu Met Ser Gly Ser Leu Leu Lys Arg Arg Pro
        195                 200                 205

Gln Gly Glu Gly Pro Asn Pro Val Ala Gly Ser Trp Glu Pro Pro Lys
    210                 215                 220

Ala His Pro Tyr Phe Pro Asp Leu Val Gln Pro Leu Leu Pro Ile Ser
225                 230                 235                 240

Gly Asp Val Ser Pro Val Ser Thr Gly Leu Pro Ala Ala Pro Val Leu
                245                 250                 255

Glu Ala Gly Val Pro Gln Gln Gln Ser Pro Leu Asp Leu Thr Arg Glu
            260                 265                 270

Pro Gln Leu Glu Pro Gly Glu Gln Ser Gln Val Ala His Gly Thr Asn
        275                 280                 285

Gly Ile His Val Thr Gly Gly Ser Met Thr Ile Thr Gly Asn Ile Tyr
    290                 295                 300

Ile Tyr Asn Gly Pro Val Leu Gly Gly Pro Pro Gly Pro Gly Asp Leu
305                 310                 315                 320

Pro Ala Thr Pro Glu Pro Pro Tyr Pro Ile Pro Glu Glu Gly Asp Pro
                325                 330                 335

Gly Pro Pro Gly Leu Ser Thr Pro His Gln Glu Asp Gly Lys Ala Trp
            340                 345                 350

His Leu Ala Glu Thr Glu His Cys Gly
        355                 360
```

<210> 388
<211> 105
<212> PRT
<213> Homo sapien

<400> 388

Met Ala Lys Ile Ser Ser Pro Thr Glu Thr Glu Arg Cys Ile Glu Ser
1 5 10 15

Leu Ile Ala Val Phe Gln Lys Tyr Ala Gly Lys Asp Gly Tyr Asn Tyr
20 25 30

Thr Leu Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Thr Glu Leu Ala
35 40 45

Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu Asp Arg Met Met
50 55 60

Lys Lys Leu Asp Thr Asn Ser Asp Gly Gln Leu Asp Phe Ser Glu Phe
65 70 75 80

Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu
85 90 95

Lys Ala Val Pro Ser Gln Lys Arg Thr
100 105

<210> 389
<211> 71
<212> PRT
<213> Homo sapien

<400> 389

Met Ala Arg Tyr Glu Glu Val Ser Val Ser Gly Phe Glu Glu Phe His
1 5 10 15

Arg Ala Val Glu Gln His Asn Cys Trp Lys Asp Pro Asn Asn Asp Phe
20 25 30

Arg Lys Asn Leu Lys Val Thr Ala Val Pro Thr Leu Leu Lys Tyr Gly
35 40 45

Thr Pro Gln Lys Leu Val Glu Ser Glu Cys Leu Gln Ala Asn Leu Val
50 55 60

Glu Met Leu Phe Ser Glu Asp
65 70

<210> 390
<211> 243
<212> PRT
<213> Homo sapien

<400> 390

Gln Thr Leu Pro Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp
1 5 10 15

Met Asp Asp Glu Asp Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile
20 25 30

Asp Ser Asn Asp Ser Asp Asp Val Asp Asp Thr Asp Asp Ser His Gln
35 40 45

Ser Asp Glu Ser His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp
50 55 60

Phe Pro Thr Asp Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro
65 70 75 80

Thr Val Asp Thr Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu
85 90 95

Arg Ser Lys Ser Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp
100 105 110

Ala Thr Asp Glu Asp Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn
115 120 125

Gly Ala Tyr Lys Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser
130 135 140

Asp Trp Asp Ser Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp
145 150 155 160

Asp Gln Ser Ala Glu Thr His Ser His Arg Gln Ser Arg Leu Tyr Lys
165 170 175

Arg Lys Ala Asn Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser
180 185 190

Gln Glu Leu Ser Lys Val Ser Arg Glu Phe His Ser His Glu Phe His
195 200 205

Ser His Glu Asp Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp
210 215 220

Lys His Leu Lys Phe Arg Ile Ser His Glu Leu Asp Ser Ala Ser Ser
225 230 235 240

Glu Val Asn

<210> 391
<211> 363
<212> PRT
<213> Homo sapien

<400> 391

Met Lys Thr Leu Leu Leu Leu Leu Leu Val Leu Leu Glu Leu Gly Glu
1 5 10 15

Ala Gln Gly Ser Leu His Arg Val Pro Leu Arg Arg His Pro Ser Leu
20 25 30

Lys Lys Lys Leu Arg Ala Arg Ser Gln Leu Ser Glu Phe Trp Lys Ser
35 40 45

His Asn Leu Asp Met Ile Gln Phe Thr Glu Ser Cys Ser Met Asp Gln
50 55 60

Ser Ala Lys Glu Pro Leu Ile Asn Tyr Leu Asp Met Glu Tyr Phe Gly
65 70 75 80

Thr Ile Ser Ile Gly Ser Pro Pro Gln Asn Phe Thr Val Ile Phe Asp
85 90 95

Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Val Tyr Cys Thr Ser Pro
100 105 110

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Val Gly Gln Gln Phe Gly Glu Ser Val Thr Glu Pro Gly Gln Thr Phe
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Leu Val Asp Leu Pro Met Phe Ser Val Tyr Met Ser Ser Asn Pro Glu
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Gln Ile Ala Leu Asp Asn Met Leu Trp Ser Val Pro Thr Leu Thr Ser
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Cys Arg Met Ser Pro Ser Pro Leu Thr Glu Ser Pro Ile Pro Ser Ala
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Gln Leu Pro Thr Pro Tyr Trp Thr Ser Trp Met Glu Cys Ser Ser Ala
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Pro Leu Pro Ala Leu Ala Met Pro Ser Pro Pro Thr Gly Val Gly Ser
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<213> Homo sapien

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Asp Cys Val Ala Phe Gly Lys Gly Glu Asn Ala Lys Lys Tyr Leu Arg
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Thr Asp Asp Arg Val Glu Arg Val Arg Ser His Cys Lys Ala Val Thr
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Ile Ser Ile Phe Glu Arg Gln Ser Gln Asn Gly Ala Thr Asn Glu Val
85 90 95

Lys Ser Met Leu Tyr Arg Val Gln Gln Leu Lys Leu Ile His Thr His
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Met Glu Gln Leu Thr Lys Asp Leu Arg Ala His Leu Asn Asp Leu Glu
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Asn Ile Ile Pro Phe Leu Gly Ile Gly Leu Leu Tyr Ser Leu Ser Gly
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Pro Asp Pro Ser Thr Ala Ile Leu His Phe Arg Leu Phe Val Gly Thr
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Arg Ile Tyr His Thr Ile Ala Tyr Leu Thr Thr Pro Leu Arg Gln Gln
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Pro Ser Pro His Ile Tyr
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/013311 A3

(54) Title: COMPOSITIONS AND METHODS RELATING TO OVARIAN SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acid molecules and polypeptides present in normal and neoplastic ovarian cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions containing the nucleic acid molecules, polypeptides, antibodies, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating ovarian cancer and noncancerous disease states in ovarian, identifying ovarian tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered ovarian tissue for treatment and research.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/24669

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-6,8-10,16 and 18

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/24669

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) : C12Q 1/68; C07H 21/04
US CL : 435/6; 91.2; 536/23.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6; 91.2; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: Medline, Biosis, Caplus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/0039760 A1 (WONG et al.) 04 April 2002 (.04.04.2002), SEQ ID NO: 193	1-6, 8-10,16, and 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
23 January 2006 (23.01.2006)

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Form PCT/ISA/210 (second sheet) (July 1998)

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group 1, claims 1-6, 8-10, 16, and 18, drawn to isolated nucleic acid molecules, vector, host cells containing, method for producing a protein encoded by the isolated nucleic acids, vaccines consisting of a nucleic acid, and kits containing the isolated nucleic acids.

Group 2, claims 11, 12, 16, 18, drawn to isolated polypeptides, vaccines consisting of polypeptides and kits containing polypeptides.

Group 3, claim 13, drawn to antibodies.

Group 4, claims 14, 15, and 17 drawn to a method for determining the presence of an ovarian specific protein and treatment with administration of a polypeptide.

Group 5, claims 7, 15 and 17 drawn to a method for determining the presence of an ovarian specific nucleotide by which ovarian cancer in diagnosed or monitored, and treating a patient with ovarian cancer through administration of the same polynucleotides.

Further species election required:

For all groups, the species in each group are considered each of the 397(SEQ ID NO: 249-396 and 1-248) separately recited polynucleotides encoding, polynucleotides, polypeptides, and antibodies recited within the claims.

The first named invention which will be searched is Group 1, claims 1-6, 8-10, 16, and 18, with respect to the first named species which is the polynucleotide of SEQ ID NO: 1.
The inventions listed as Groups 1-5 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature that joins all of these inventions is the nucleic acids recited in the claim that encode proteins. However, the an isolated nucleic acid molecule comprising a nucleic acid molecule that selectively hybridizes to the nucleic acid sequence of SEQ ID NO: 7 was known at the time the invention was made as taught by US20020039760A1 and Wong et al. in their SEQ ID NO: 193 that shares 90.6% identity to present SEQ ID NO: 7 and as a result could hybridize to the claimed sequence and thus, this is not a special technical feature in view of the PCT rules. Group 1 is the first named invention including isolated polynucleotides. Group 2 includes polypeptides encoded by Group I's nucleic acids. There is no special technical feature that joins the first named products as the isolated nucleic acid of groups 1 and 2 is anticipated in the prior art. The remaining groups include additional products and methods that are not linked by a unifying inventive concept as they are drawn to unique products and methods and are so separately grouped.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each is drawn to a unique nucleic acid sequence that does not share a common structure with the others.